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Research paper

The mediating effect of stress reactivity in the 18-year bidirectional relationship between generalized anxiety and depression severity

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ABSTRACT

Background: Generalized anxiety disorder (GAD) and major depressive disorder (MDD) often precede and predict one another. Heightened stress reactivity may be a mediation mechanism underlying the long-term connections between GAD and MDD. However, cross-sectional studies on this topic have hindered directional inferences.
Method: The present study examined stress reactivity as a potential mediator of the sequential associations between GAD and MDD symptoms in a sample of 3,294 community-dwelling adults (M age = 45.6, range = 20–74). Participants completed three waves of measurement (T1, T2, and T3) spaced nine years apart. GAD and MDD symptom severity were assessed at T1, T2, and T3 (Composite International Diagnostic Interview-Short Form). Stress reactivity (Multidimensional Personality Questionnaire) was measured at T2.
Results: Structural equation mediation modeling demonstrated that higher T1 GAD symptoms positively predicted more severe T3 MDD symptoms via T2 stress reactivity, controlling for T1 MDD (d = 0.45–0.50). However, T2 stress reactivity was not a significant mediator in the relationship between T1 MDD severity and T3 GAD symptoms after controlling for T1 GAD. Direct effects indicated that T1 GAD positively predicted T3 MDD 18 years later and vice versa (d = 1.29–1.65).
Limitations: Stress reactivity was assessed using a self-report measure, limiting conclusions to perceived (vs. physiologically indexed) stress reactivity.
Conclusions: These findings indicate that stress reactivity may be one mechanism through which GAD leads to later MDD over prolonged durations. Overall, results suggest that targeting stress reactivity in treatments for GAD may reduce the risk of developing subsequent MDD.

1. Introduction

Generalized anxiety disorder (GAD) and major depressive disorder (MDD) are common and comorbid mental health problems with overlapping symptoms of fatigue, irritability, sleep disruption, and concentration difficulties. It is estimated that 60–70 % of individuals with an anxiety disorder meet diagnostic criteria for a lifetime depressive disorder and vice versa (Brown et al., 2001; Kessler et al., 2005; Lamers et al., 2011). Experiencing comorbid GAD and MDD compared to either disorder alone has been associated with greater severity of both diagnoses, poorer treatment response, and overall decreased quality of life (Dold et al., 2017; Norberg et al., 2008; Penninx et al., 2011). Moreover, GAD and MDD are bidirectional risk factors for each other at both the symptom and disorder levels (see meta-analysis by Jacobson and Newman, 2017). Such reciprocal connections between heightened GAD and MDD have been observed consistently over more than a decade (Fichter et al., 2010; Kessler et al., 2008; Moffitt et al., 2007; Neufeld et al., 1999). For example, individuals with anxiety disorders were more likely to have MDD ten years later (Gustavson et al., 2018; Kessler et al., 2008), and MDD similarly predicted future GAD (Kessler et al., 2008; Klein et al., 2011). Further, pure anxiety symptoms predicted future depressive symptoms across 25 years (Fichter et al., 2010). Thus, improving understanding of the long-term relationship between GAD and MDD symptoms is essential.

Stress reactivity may be one factor underlying the connection between GAD and MDD. The concept of stress reactivity refers to an individual disposition to respond to stressful situations and demands with immediate, acute, and long-lasting emotional reactions (Limm et al.,

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2010; Schlotz et al., 2011; Schulz et al., 2005). Notably, intense affective stress responses have been conceptualized as an essential vulnerability feature contributing to future psychopathology (Almeida, 2005). Over time, patterns of heightened emotional responses to stressors could lead to the development of GAD and MDD, disorders characterized by prolonged emotion dysregulation and negative affect (Hammen, 2005; Newman et al., 2013). Indeed, individuals vulnerable to intense, prolonged stress reactions would have difficulty regulating negative affect in stressful situations. This may lead to maladaptive coping strategies (e.g., worry, rumination, avoidance) to manage unpleasant feelings in response to stressors. These counter-productive tendencies often intensify negative emotions and were reliably associated with anxious and depressive symptoms (Iqbal and Dar, 2015; Jiaxuan et al., 2018; Koval et al., 2012; Starr et al., 2016). Over long durations, exaggerated stress responses and subsequent prolonged negative emotionality could plausibly lead to and exacerbate symptoms of GAD and MDD.

Thus far, seven longitudinal studies have observed that heightened stress reactivity and similar constructs preceded and predicted elevated anxiety and depression symptoms. Two studies of university students found that greater emotional reactivity to stressful interpersonal and non-interpersonal events predicted depression symptoms two months later (O'Neill et al., 2004; Parrish et al., 2011). Similarly, stress sensitivity was linked to depressive symptoms after one year in a sample of twins (Wichers et al., 2009). Moreover, community adults who reported a more dramatic drop in positive emotions in response to stress, experienced more severe depressive symptoms after an 18-month interval (Zhaoyang et al., 2019). Exaggerated appraisal of stressor severity also predicted worse anxiety and depressive symptoms five years later in young adults at risk for internalizing disorders (Conway et al., 2016). In addition, level of prolonged stress reactivity was a significant predictor of anxious and depressive symptoms seven years later in a study of industrial workers (Herr et al., 2018). Lastly, in a study that combined daily diary and cross-panel designs, lower positive emotions on stressful days predicted more severe depression and anxiety seven years later (Rackoff and Newman, 2020). These collective findings suggest that stress reactivity may be a crucial trait-level factor influencing the course of anxiety and depressive symptoms over long periods.

Simultaneously, *scar* models propose that experiencing more severe GAD and MDD symptoms may have long-term effects on certain individual dispositions. Considering these theories, anxiety and depression could impact trait stress reactivity in the long term (Allemand et al., 2020; Lewinsohn et al., 1981; Rohde et al., 1990). For instance, as anxiety and depression are theorized to be disorders of emotion dysregulation, dysfunctional emotional response patterns in individuals with elevated GAD and MDD could contribute to increased trait stress reactivity over prolonged durations (Cludius et al., 2020; Fernandez et al., 2016). More specifically, anxiety disorders are characterized by heightened attention to potential threats and hyperreactivity to stressful experiences (Conway et al., 2016; Goodwin et al., 2017; Hyde et al., 2019; Llera and Newman, 2010). Individuals with GAD interpreted neutral situations as negative or stressful (Aue and Okon-Singer, 2015; Hirsch et al., 2016; Mathews et al., 1997) and reported difficulty regulating emotions when distressed (Salters-Pedneault et al., 2006; Turk et al., 2005). Therefore, it is plausible that GAD could lead to a tendency to perceive more situations as stressful and exhibit intense reactions to these events. Moreover, GAD was linked to intolerance of uncertainty, which could lead to exaggerated responses to unexpected stressors (McEvoy and Mahoney, 2012). Additionally, heightened worry is a crucial feature of GAD. The elevated state of distress created by worrying could make minimally stressful situations feel less tolerable and trigger more intense reactions.

Findings from empirical studies support the idea that experiencing anxiety symptoms could contribute to elevated levels of stress reactivity in the future. For example, a six-year study of adolescents indicated that social anxiety symptoms were related to high self-reported and physiologically-measured stress reactivity (Nelemans et al., 2017). In another social anxiety study, anxious symptoms were significantly associated with heightened reactions to psychological stressors (Yoon and Joormann, 2012). Moreover, in a laboratory-based experiment, youth with anxiety demonstrated heightened adverse emotional responses to a stressor task (Carthy et al., 2010). Youth with GAD also reported stronger negative emotions and elevated physiological reactivity to stressful events in an hour-to-hour context (Tan et al., 2012). In adults, anxiety symptoms similarly predicted more severe dynamic emotional shifts in response to a stress induction (Egan and Dennis-Tiwary, 2018). Thus, considering scar models and these previous findings, higher stress reactivity may result from experiencing heightened GAD symptoms across long durations.

Experiencing depression symptoms for long durations could also impact stress reactivity. For instance, it has been hypothesized that experiencing depression symptoms could potentially lead to blunted stress reactivity. The *emotional context insensitivity theory* postulates that MDD can result in diminished emotional responses to stressors, rather than hyperreactivity (Burke et al., 2005; Bylsma, 2021; Rottenberg, 2007). In line with this, earlier laboratory-based research found that MDD was associated with dampened emotional responses to negative and positive stimuli (for review, see Bylsma et al., 2008). However, other experimental and observational studies showed that persons with depression rated stressful events and responded more unproductively to stressors than healthy controls (Bylsma et al., 2011; Hamilton and Alloy, 2016).

Further, more recent literature suggests that depression symptoms are intertwined with *heightened* emotional reactions to stressors across time (Connolly and Alloy, 2017; Lamers et al., 2018; Sheets and Armey, 2020; Zhaoyang et al., 2019). Plausibly, MDD could lead to elevated stress reactivity as a scarring effect (Wichers et al., 2010). For instance, cognitive theories of depression posit that MDD is maintained by negative attentional bias and patterns of distorted cognitions (e.g., catastrophizing), features that could increase reactivity to perceived stressors over time (Hindash and Amir, 2012; Joormann and Vanderlind, 2014; Lewinsohn et al., 1981; Winer and Salem, 2016). In line with these theories, research findings support the notion that MDD can contribute to heightened stress reactivity in the future. For example, adults with chronic depression showed more extreme affective reactions to negative stimuli (Guhn et al., 2018). Patients with remitted MDD also reported high reactivity to social stress compared to participants with no depression history (van Winkel et al., 2015). Similarly, individuals with a history of MDD demonstrated more intense emotional responses to everyday stressors (Husky et al., 2009; O'Hara et al., 2014). Considering these findings, higher stress reactivity could be a consequence of experiencing heightened MDD symptoms for extended durations.

The theories and data above suggest that stress reactivity is a candidate mediator in the relationship between GAD predicting future MDD symptoms in the long term, and potentially vice versa. Determining the factors mediating the prospective association between GAD and later MDD is essential for several reasons. Considering that anxiety and depressive disorders often lead to one another over long periods (Fichter et al., 2010; Gustavson et al., 2018; Jacobson and Newman, 2017; Merikangas et al., 2003), understanding how risk factors may contribute to these longitudinal connections could provide opportunities for prevention and guide treatment efforts. Clarifying the role of stress reactivity in this relationship may also refine the understanding of comorbidity and identify potential avenues for new research. Moreover, the present study added to prior literature that examined specific mechanisms that mediated prospective pathway between anxiety and depression. Mediators of the anxiety-depression prospective relation identified thus far include brooding tendencies (McLaughlin and Nolen-Hoeksema, 2011), avoidance (Jacobson and Newman, 2014), relationship problems (Jacobson and Newman, 2016; Starr et al., 2014; Barber et al., 2023), and social criticism (Lord et al., 2020). Other notable mediators include threat-related attentional biases (Price et al., 2016), subjective appraisals of close and group relationships (Jacobson and

Newman, 2016), sleep troubles (Li et al., 2018; Nguyen et al., 2022), need for cognition (Zainal and Newman, 2022, 2023), and excessive focus on emotions and venting (Marr et al., 2022). Our study thus extends the extant research by testing the potential mediating role of stress reactivity in the pathways between GAD and MDD symptoms in a sample of community-dwelling adults.

As past research indicates that the connections between comorbid anxiety and depression disorders often unfold over prolonged periods, it is essential to understand mechanisms that may underlie these long-term associations. Accordingly, the current study examined if stress reactivity mediated the bidirectional relationship between GAD and MDD severity across 18 years. We utilized a longitudinal sample of community adults who participated in three waves of data collection (T1, T2, and T3) spaced approximately nine years apart. Based on stress reactivity theories and the evidence above, we hypothesized: (a) more severe GAD symptoms at baseline (T1) would predict worse MDD symptoms 18 years later at T3 (Hypothesis 1); (b) higher T1 MDD symptom severity would similarly predict more severe T3 GAD symptoms (Hypothesis 2); (c) the relationship between T1 GAD symptoms and T3 MDD symptoms would be significantly mediated by Time 2 (T2) stress reactivity (assessed about nine years following T1), such that more severe T1 GAD symptoms would predict higher T2 stress reactivity, which would then lead to worse T3 MDD symptoms (Hypothesis 3); and (d) the relationship between T1 MDD symptoms and future T3 GAD symptoms would also be substantially mediated by T2 stress reactivity, such that elevated T1 MDD symptoms would predict T2 higher stress reactivity, and therefore result in increased T3 GAD symptoms (Hypothesis 4).

2. Method

2.1. Participants

Data for the present study were drawn from the Midlife Development in the United States (U.S.) (MIDUS) study (Brim et al., 2019; Ryff et al., 2017; Ryff et al., 2019). The MIDUS study consists of three waves of data collection: MIDUS I (1995 to 1996; T1); MIDUS II (2004 to 2006; T2); and MIDUS III (2012 to 2013; T3) (Brim et al., 2019; Ryff et al., 2017; Ryff et al., 2019). The present sample consists of 3,294 adults who participated in three waves of assessment for data collection. Average age at T1 was 45.6 years (SD = 11.4, range = 20 to 74). Of these participants, 54.6 % were female, 89 % identified their ethnicity as White, and 46.8 % had a college degree. Table 1 displays the sample demographic data, descriptive statistics, and correlation matrix of the study variables.

2.2. Procedures

Past 12-month symptom severity for MDD and GAD were determined using the Composite International Diagnostic Interview–Short Form (CIDI-SF; Kessler et al., 1998; Wittchen et al., 1994). The self-report Multidimensional Personality Questionnaire (MPQ)-Stress Reactivity subscale (Patrick et al., 2002) was administered at T2.

2.3. Measures

2.3.1. Stress reactivity

Stress reactivity was assessed using the 3-item MPQ-Stress Reactivity subscale (Patrick et al., 2002). Sample items include "My mood often goes up and down" and "Minor setbacks sometimes irritate me too much." Participants responded by rating the extent to which each item generally described them on a 4-point Likert-type scale (1 = *false* to 4 = *true of you*). Scores were calculated by summing responses to each item, and higher scores indicated greater stress reactivity. The MPQ-Stress Reactivity subscale had good internal consistency (Cronbach's α = 0.74), convergent and discriminant validity, and retest reliability (Patrick et al., 2002; Tellegen and Waller, 2008). In this study, internal consistency was good (α = 0.74).

2.3.2. Generalized anxiety disorder symptom severity

GAD severity was measured at each wave of MIDUS data collection using the CIDI-SF (Kessler et al., 1998; Wittchen et al., 1994) that was based on the revised Diagnostic and Statistical Manual of Mental Disorders (3rd ed., rev.; DSM–III–R; American Psychiatric Association, 1987). Participants received this interview if they met the pre-screening conditions by responding that they worried "a lot more" than most people, worried "every day, just about every day, or most days," and worried about "more than one thing" or had different worries "at the same time." Ten items reflective of DSM–III–R GAD criteria were used to assess GAD severity. Participants indicated how frequently over the past 12 months they had experienced each item by using a four-point Likert scale (1 = *never* to 4 = *on most days*). Examples of items included "were restless because of your worry," "had trouble keeping your mind on what you were doing," and "were keyed up, on edge, or had a lot of nervous energy." A severity score was calculated by taking the sum of "on most days" responses to the items so that a higher score indicated a higher level of GAD. A comparison of diagnostic classifications between the short-form and full-length CIDI showed high levels of specificity (99.8 %) and sensitivity (96.6 %) of the CIDI-SF for GAD (Kessler et al., 1998). In our study, the CIDI-SF for GAD showed high internal

Table 1
Correlation matrix of study variables.

	1	2	3	4	5	6	7	8
1. Age	–							
2. Gender (female)	0.031	–						
3. Ethnicity	−0.063*	0.120	–					
4. T1 GAD	−0.054	0.333***	0.074	–				
5. T1 MDD	−0.028***	0.138***	0.128	0.567***	–			
6. T2 SR	−0.106***	0.013	−0.059	0.263***	0.182***	–		
7. T3 GAD	−0.047	0.175***	0.183**	0.506***	0.381***	0.284***	–	
8. T3 MDD	−0.060***	0.132***	0.090**	0.346***	0.400***	0.150***	0.604***	–
M or *n*	45.62	1799	2932	21.8	0.28	6.13	22.2	0.25
SD or %	11.41	54.61	89.01	6.35	0.73	2.24	6.90	0.70
Min	20			10	0	3	10	0
Max	74			40	2.75	12	40	2.75
Skewness	0.24	4.29	5.26	0.70	2.40	0.32	0.59	2.64
Kurtosis	−0.70	38.8	28.50	−0.11	4.13	−0.68	−0.43	5.40

GAD = generalized anxiety disorder; MDD = major depressive disorder; SR = stress reactivity; T1 = time 1; T2 = time 2 (9 years after T1) T3 = time 3 (9 years after T2 and 18 years after T1).
*** $p < .001$.
** $p < .01$.
* $p < .05$.

consistency (0.87 at T1 and 0.89 at T3).

2.3.3. Major depression disorder symptom severity

MDD symptom severity was similarly measured using the DSM–III–R-aligned CIDI-SF (Kessler et al., 1998; Wittchen et al., 1994). The CIDI-SF assesses for the presence of seven symptoms related to depressed affect or anhedonia during two weeks over the past 12 months. Such symptoms included "losing interest in most things," "having more trouble concentrating than usual," and "feeling down on yourself, no good, or worthless." Responses to each item were summed to calculate an MDD severity score, of which a higher score endorsed more severe depression levels. A comparison of diagnostic classifications between the brief and complete CIDI diagnostic tests for MDD showed that the CIDI-SF had high levels of specificity (93.9 %) and sensitivity (89.6 %) (Kessler et al., 1998). This current study's internal consistency of the CIDI-SF for MDD was excellent (0.93 at T1 and T3).

2.4. Data analyses

For all data analyses, we used the *R* (Version 4.1.0) and *RStudio* (Version 1.4.1717) (R Core Team, 2021) software. To preprocess the data, we determined that all variables of interest had acceptable skewness values of $\leq\pm3$ and kurtosis values of $\leq\pm7$, and we detected no outliers. Longitudinal confirmatory factor analyses and structural equation mediation model analyses were performed using the *R* package *lavaan* (Rosseel, 2012) with the *RStudio* software (Version 4.0.3). Analyses were conducted using maximum likelihood with robust standard error estimators to accommodate any univariate or multivariate non-normal distributions in the data set (Li, 2016). Model fit was assessed using the confirmatory fit index (CFI) (Hu and Bentler, 1999), root mean square error of approximation (RMSEA), and standardized root mean square residual (SRMR) (Hu and Bentler, 1998).

A longitudinal measurement invariance test was conducted using a series of confirmatory factor analyses (CFA) to measure the equivalence of measures across time points. This approach determines the degree to which assessments had comparable measurement properties across each assessment wave (Widaman et al., 2010). Specifically, we evaluated *configural* (similar factor structure), *metric* (equal factor structure and item loadings (λs), freely estimated item intercepts (τs), and item error variances (εs) across each time point), *scalar* (equal factor structure, λs and τs, across each time point, but freely varying εs), and *strict* (equivalent factor structure, λs, τs, and εs, across each time point) levels of invariance (Cheung and Rensvold, 2002). Change in χ^2 ($\Delta\chi^2$) difference tests with a Sattorra-Bentler scaling correction factor were conducted to assess for measurement invariance (Satorra and Bentler, 2010), with a statistically significant $\Delta\chi^2$ indicating that the more restricted model had a worse model fit. However, the $\Delta\chi^2$ can be easily statistically significant despite negligible misfit change as it is sensitive to large sample sizes. Thus, invariance was considered to be established if ΔCFI ≤ -0.010, ΔRMSEA $< +0.015$, or ΔSRMR $< +0.030$ between the less and more restricted models when adding constraints (Chen, 2007; Van Doren et al., 2021; Zainal et al., 2021).

Structural models were used to test the direct effects of GAD on future MDD symptom severity and vice versa. The first direct effect model included a path from T1 GAD symptom severity predicting T3 MDD symptom severity. The second direct effect model examined the association of T1 MDD symptoms and T3 GAD severity. Next, structural models were examined that included stress reactivity as a mediator. The first mediation model had paths from T1 GAD symptoms predicting T2 stress reactivity to T3 MDD symptoms as the outcome variable. The second mediation model included T1 MDD symptoms as a predictor of T2 stress reactivity and had T3 GAD symptoms as the outcome. We used a product-of-coefficients (a × b) approach to the indirect effects of the mediation analyses. A mediation analysis was conducted for the regression coefficients of T1 GAD symptom severity predicting the mediator T2 stress reactivity (*a* path) and T2 stress reactivity predicting T3 MDD severity (*b* path). A second mediation analysis included the regression coefficients of T1 MDD severity forecasting T2 stress reactivity (*a* path) and T2 stress reactivity predicting T3 GAD severity (*b* path). We presented the unstandardized regression coefficients and 95 % confidence intervals and used bootstrapping with 10,000 resampling draws. The mediation effect size was represented by the proportion of the indirect effect ($a \times b$) relative to the total effect ($c = a^*b + c'$), expressed as a percentage of variance wherein T2 stress reactivity accounted for the relationship between T1 GAD predicting T3 MDD, or T1 MDD predicting T3 GAD.

For a robust test of our analyses, we then repeated the mediation analyses adjusting for the outcome variables at baseline for statistical (Maxwell and Cole, 2007) and theoretical (de Rooij et al., 2010) reasons. Similarly, based on the literature, we adjusted for each of the following baseline covariates separately: age (Neupert et al., 2007; Schlotz et al., 2011), gender (Schlotz et al., 2011; Verma et al., 2011), income (Grzywacz et al., 2004), and education (Grzywacz et al., 2004; Limm et al., 2010). However, we did not control for T1 stress reactivity because researchers well-versed in the study of causal inference and investigations suggest that controlling for a mediating variable at baseline may mistakenly bias the estimation of total effects as controlling for the same may block part of the causal effect through the mediator (D'Onofrio et al., 2020; Rosenbaum, 1984). We also did not include any T2 covariates, as such controls would bias the direct and mediation effect estimation and would impede detecting part of the potential causal effect via the mediator (D'Onofrio et al., 2020; Rosenbaum, 1984). Further, we did not include T3 MDD or GAD as a covariate (i.e., conduct a cross-lagged panel model analysis). This is because adjusting for cross-sectional outcome variables biases the parameter estimates of the mediation analysis (Wu et al., 2018), affects the temporal ordering of the variables in the causal chain of analysis (Fairchild and McDaniel, 2017), and is not theoretically justifiable (Bullock and Green, 2021).

Missing data (approximately 20.34 % missing of all observations across 18 years and three assessment waves) were handled using full information maximum likelihood (FIML), with missing data assumed to be missing at random (Graham, 2009). Furthermore, Little's Missing Completely at Random Test (MCAR) was statistically non-significant (χ^2 ($df = 34$) = 45.90, $p = .084$). FIML has been established as an efficient and unbiased method to handle missing data in longitudinal SEM (Lee and Shi, 2021). Cohen's *d* effect size was computed to determine the magnitude of the effects. The formula ($d = 2t / \sqrt{(df)}$) was used (Dunst et al., 2004), where values of 0.2, 0.5, and 0.8 signified small, moderate, and large effect sizes, respectively.

3. Results

3.1. Longitudinal measurement invariance

Tables S1 and S2 in the online Supplementary materials (OSM) display the longitudinal measurement invariance analyses for the constructs of interest in the current study. Analyses showed a strict equivalence level (equal λs, τs, εs) was observed for the GAD and MDD symptom severity constructs. Thus, conducting longitudinal structural equation mediation modeling was appropriate for the current data set.

3.2. Structural equation mediation models

3.2.1. T1 GAD predicting T3 MDD severity

The structural model for T1 GAD predicting T3 MDD severity showed good fit ($\chi^2(df = 101) = 416.41$, $p < .001$, CFI = 0.97, RMSEA = 0.05, SRMR = 0.04). Supporting Hypothesis 1, higher T1 GAD symptoms significantly positively predicted T3 MDD severity ($b = 0.08$, 95 % CI [0.06, 0.11], $p < .001$, $d = 1.29$).

3.2.2. T1 MDD predicting T3 GAD severity

The model of T1 MDD leading to T3 GAD symptoms showed good

model fit ($\chi^2(df = 101) = 296.35$, $p < .001$, CFI = 0.98, RMSEA = 0.03, SRMR = 0.03). Consistent with Hypothesis 2, the direct path of more severe T1 MDD predicting higher T3 GAD severity was significant (b = 1.17, 95 % CI [0.89, 1.44], $p < .001$, $d = 1.65$).

Table 2
Mediation model of T1 GAD predicting T3 MDD via T2 stress reactivity, controlling for T1 MDD.

	Estimate	95 % CI	Cohen's *d*
Regressions			
$(GAD)_{[T1]}$ ➔ $(MDD)_{[T3]}$	0.039*	[0.006, 0.073]	0.361
$(GAD)_{[T1]}$ ➔ $(SR)_{[T2]}$	0.388***	[0.271, 0.504]	1.018
$(SR)_{[T2]}$ ➔ $(MDD)_{[T3]}$	0.047***	[0.022, 0.072]	0.568
$(MDD)_{[T1]}$ ➔ $(MDD)_{[T3]}$	0.035***	[0.016, 0.053]	0.570
Covariances			
$(MDD)_{[T1]}$ ~~ $(GAD)_{[T1]}$	0.311***	[0.256, 0.367]	1.709
Factor loadings			
T1 GAD 1	1.000***	[1.000, 1.000]	–
T1 GAD 2	0.856***	[0.760, 0.952]	2.729
T1 GAD 3	0.947***	[0.821, 1.074]	2.296
T1 GAD 4	0.927***	[0.809, 1.046]	2.394
T1 GAD 5	1.052***	[0.922, 1.181]	2.488
T1 GAD 6	0.982***	[0.858, 1.106]	2.423
T1 GAD 7	1.039***	[0.892, 1.186]	2.160
T1 GAD 8	1.056***	[0.901, 1.210]	2.096
T1 GAD 9	1.227***	[1.072, 1.383]	2.414
T1 GAD 10	0.915***	[0.765, 1.064]	1.874
T3 MDD 1	1.000***	[1.000, 1.000]	–
T3 MDD 2	0.397***	[0.362, 0.432]	3.475
T3 MDD 3	0.755***	[0.681, 0.829]	3.121
T3 MDD 4	0.913***	[0.866, 0.959]	5.971
T3 MDD 5	0.701***	[0.622, 0.779]	2.728
T3 MDD 6	0.680***	[0.599, 0.761]	2.567
T2 SR 1	1.000***	[1.000, 1.000]	–
T2 SR 2	0.990***	[0.831, 1.149]	1.903
T2 SR 3	1.055***	[0.893, 1.216]	2.002
Residual variances			
T1 GAD 1	0.383***	[0.327, 0.438]	2.109
T1 GAD 2	0.498***	[0.435, 0.562]	2.411
T1 GAD 3	0.406***	[0.355, 0.458]	2.428
T1 GAD 4	0.663***	[0.592, 0.734]	2.849
T1 GAD 5	0.613***	[0.543, 0.684]	2.659
T1 GAD 6	0.388***	[0.338, 0.439]	2.355
T1 GAD 7	0.435***	[0.378, 0.492]	2.338
T1 GAD 8	0.584***	[0.511, 0.656]	2.458
T1 GAD 9	0.492***	[0.426, 0.557]	2.292
T1 GAD 10	0.764***	[0.684, 0.843]	2.947
T3 MDD 1	0.002**	[0.001, 0.003]	0.508
T3 MDD 2	0.002***	[0.001, 0.002]	1.105
T3 MDD 3	0.009***	[0.007, 0.011]	1.233
T3 MDD 4	0.004***	[0.002, 0.006]	0.684
T3 MDD 5	0.009***	[0.007, 0.011]	1.423
T3 MDD 6	0.010***	[0.008, 0.012]	1.509
T2 SR 1	0.507***	[0.427, 0.586]	1.947
T2 SR 2	0.461***	[0.394, 0.529]	2.089
T2 SR 3	0.394***	[0.328, 0.460]	1.823
Residual variances			
Variance of $(GAD)_{[T1]}$	0.341***	[0.271, 0.410]	1.498
Variance of $(MDD)_{[T3]}$	0.030***	[0.026, 0.033]	2.482
Variance of $(SR)_{[T2]}$	0.336***	[0.264, 0.407]	1.433
Variance of $(MDD)_{[T1]}$	0.892***	[0.802, 0.982]	3.044
Defined parameters			
Indirect effect	0.018**	[0.007, 0.029]	0.493
Total effect	0.057***	[0.027, 0.088]	0.571

CI = confidence interval; GAD = generalized anxiety disorder severity; MDD = major depressive disorder symptom severity; SR = stress reactivity; T1 = time 1; T2 = time 2 (9 years after T1); T3 = time 3 (9 years after T2 and 18 years after T1); CFI = confirmatory fit index; RMSEA = root mean square error of approximation; SRMR = standardized root mean squared residual. Model fit indices: $\chi^2(df = 164) = 476.63$, $p < .001$, CFI = 0.974, RMSEA = 0.035, 95 % CI [0.030, 0.039], SRMR = 0.038.

*** $p < .001$.

** $p < .01$.

* $p < .05$.

3.2.3. T1 GAD predicting T3 MDD severity via T2 stress reactivity

Table 2 shows the model fit indices and parameter estimates of the model examining the mediational effect of stress reactivity on the relation between T1 GAD and T3 MDD severity. This model showed good fit ($\chi^2(df = 147) = 297.83$, $p < .001$, CFI = 0.98, RMSEA = 0.04, SRMR = 0.04). Fig. 1 displays the path analysis for this longitudinal structural equation mediation model. More severe GAD symptoms at T1 were significantly related to more severe T3 MDD symptoms (b = 0.07, 95 % CI [0.04, 0.10], $p < .001$, $d = 0.77$). Further, worse T1 GAD symptoms predicted higher T2 stress reactivity nine years later (b = 0.39, 95 % CI [0.27, 0.51], $p < .001$, $d = 1.08$). Elevated T2 stress reactivity thereby significantly predicted more severe T3 MDD symptoms (b = 0.05, 95 % CI [0.02, 0.07], $p = .001$, $d = 0.50$). Additionally, the indirect mediation path of T1 GAD severity positively predicting T3 MDD severity via T2 stress reactivity was significant (b = 0.02, 95 % CI [0.01, 0.03], $p = .002$, $d = 0.50$). T2 stress reactivity mediated 20.22 % of the variance of T1 GAD predicting T3 MDD. Also, the mediation effect of higher T1 GAD predicting worse T3 MDD severity via T2 stress reactivity stayed significant after adjusting for age, gender, education level, income, and baseline MDD symptoms (d = 0.45–0.49).

3.2.4. T1 MDD predicting T3 GAD severity via T2 stress reactivity

The model fit indices and parameter estimates of this mediation model are shown in Table 3. The mediation model displayed good fit ($\chi^2(df = 147) = 268.51$, $p < .001$, CFI = 0.98, RMSEA = 0.04, SRMR = 0.04). Fig. 2 shows the path analysis for this prospective structural equation mediation model. About the direct effect, more severe T1 MDD symptoms significantly predicted higher T3 GAD symptoms (b = 0.97, 95 % CI [0.67, 1.28], $p < .001$, $d = 1.02$). Also, heightened T1 MDD significantly predicted increased T2 stress reactivity (b = 0.82, 95 % CI [0.49, 1.16], $p < .001$, $d = 0.79$), and higher T2 stress reactivity notably forecasted greater T3 GAD severity (b = 0.24, 95 % CI [0.14, 0.33], $p < .001$, $d = 0.82$). T2 stress reactivity significantly mediated the pathway between T1 MDD and T3 GAD (b = 0.19, 95 % CI [0.08, 0.31], $p = .001$, $d = 0.56$) and explained 17 % of the association between T1 MDD and T3 GAD. After controlling for age, gender, education, and income, the mediation effect remained statistically significant (d = 0.45–0.54). However, with baseline GAD symptoms included as a covariate, the indirect effect of T2 stress reactivity on the relationship between T1 MDD and T3 GAD was no longer significant.

4. Discussion

To the best of our knowledge, this is the first study to examine stress reactivity as a potential mediator of the bidirectional relationships between GAD and MDD symptoms over 18 years. Congruent with Hypothesis 1, higher T1 GAD severity predicted more severe T3 MDD symptoms 18 years later. Further, elevated T1 MDD symptoms similarly predicted worse T3 GAD severity, supporting Hypothesis 2. These results and their large effect sizes align with evidence from prior longitudinal studies that supported a reciprocal relationship between anxiety and depressive symptoms (see meta-analysis by Jacobson and Newman, 2017). Moreover, consistent with Hypothesis 3, T2 stress reactivity significantly mediated the relationship between T1 GAD symptoms and T3 MDD severity with moderate-to-large effect sizes, after controlling for age, gender, education, income, and baseline MDD symptoms. In contrast, Hypothesis 4 was not supported as stress reactivity was not a significant mediator of the pathway between T1 MDD and future T3 GAD severity, with small-to-moderate effect sizes after controlling for baseline GAD. The present data underscore the impact of stress reactivity in the longitudinal path between GAD and future MDD severity.

The present study indicated that stress reactivity mediated the longitudinal relationship between GAD and future MDD symptom severity, with a medium effect size. These findings support stress reactivity theories, which propose that heightened emotional responses to stressors and exaggerated stress appraisals can play a salient role in the

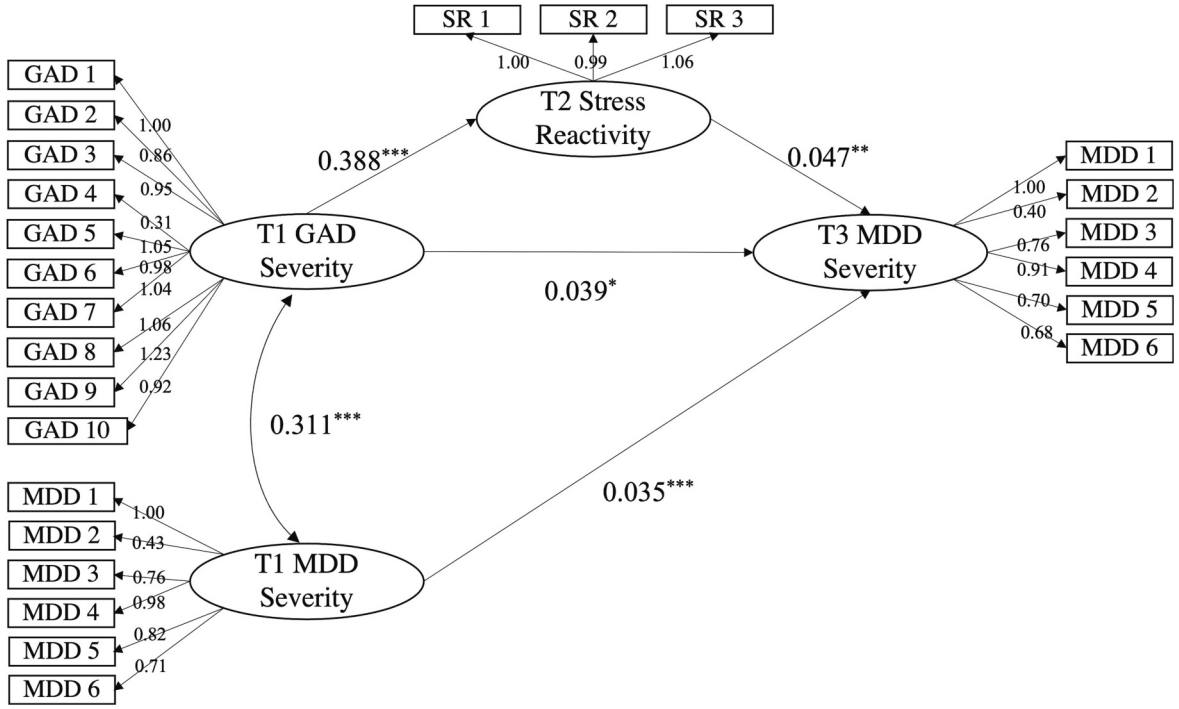

Fig. 1. Mediation model of T1 GAD predicting T3 MDD via T2 stress reactivity.
Note. ***$p < .001$; **$p < .01$; *$p < .05$.
GAD = generalized anxiety disorder, MDD = major depressive disorder.

maintenance and development of psychopathology (Fairholme et al., 2010; Schlotz et al., 2011). Our results are consistent with prior studies that demonstrated the association between GAD and stress reactivity (Carthy et al., 2010; Egan and Dennis-Tiwary, 2018; Nelemans et al., 2017; Yoon and Joormann, 2012). Moreover, the current findings align with research that indicated a connection between stress reactivity and future MDD symptoms (Charles et al., 2013; O'Neill et al., 2004; Parrish et al., 2011; Wichers et al., 2009).

Why did higher T2 stress reactivity mediate the relationship between T1 GAD and T3 MDD severity? It is possible that experiencing GAD symptoms for a long duration resulted in more intense stress reactivity as a scarring effect (Allemand et al., 2020; Lewinsohn et al., 1981; Rohde et al., 1990). For instance, GAD is characterized by hypervigilance to possible threats and acute emotional responses to adverse situations. Over time, individuals with GAD could have begun interpreting mildly stressful and even neutral events as distressing, leading to more frequent negative emotional reactions. Indeed, anxiety symptoms were linked with heightened stress responses, both by self-report and physiological measures (Aldao et al., 2013; Macatee and Cougle, 2013; Mennin et al., 2005; Mennin et al., 2009; Steinfurth et al., 2017). Moreover, the high levels of worry seen in GAD could have created a heightened state of distress and exacerbated sensitivity to stressful situations. Supporting this idea, worrying prior to a stressor increased negative reactivity from baseline (Jamil and Llera, 2021). Thus, GAD symptoms could have produced more extreme reactions to perceived stressors and higher trait stress reactivity.

As seen in the present study, persons with GAD and high stress reactivity may have been more vulnerable to future elevated MDD over long durations. As emotion dysregulation plays a crucial role in the onset and recurrence of depression, intense emotional stress responses could have given way to MDD symptoms. Further, frequent exposure to heightened negative affect in reaction to stressors could have had a "wear-and-tear" impact on emotional well-being in the long term, potentially increasing the risk of developing MDD (Cohen et al., 2005; McEwen, 1998; Patten, 2015; Zhaoyang et al., 2019). Congruent with these notions, Charles et al. (2013) found that individuals who reported increased negative affect on stressful and non-stressful days were more likely to experience depressive symptoms a decade later. Therefore, it is plausible that patterns of elevated stress reactions over long durations could have increased vulnerability to MDD symptoms.

Other characteristics of anxiety and depression could potentially explain the mediational effect of stress reactivity in the association between GAD symptoms and future MDD. For instance, GAD is often accompanied by a higher level of intolerance of uncertainty (Carleton, 2012; Jensen et al., 2016). Individuals with heightened GAD symptoms and an aversion to the unknown may have experienced amplified reactions to unexpected stressors, as reflected in the findings of this study. Over long durations, negative attitudes toward ambiguity and heightened stress reactivity could have encouraged individuals to engage in behavioral avoidance to avoid uncertain situations and possible stressors, thereby precipitating increased MDD. Excessive avoidance of unpredictable situations could have inadvertently reduced exposure to potentially rewarding and mood-uplifting events. For persons with heightened GAD and an elevated level of stress reactivity, avoidant patterns and this subsequent lack of positive life experiences may have led to more severe MDD in the future, in line with the present data. Lending credence to these ideas, intolerance of uncertainty was linked to both GAD and MDD (McEvoy and Mahoney, 2012), and avoidance has been shown to mediate the positive relationship between anxiety and depression later on (Jacobson and Newman, 2014; Moitra et al., 2008). Future prospective research could examine how stress reactivity relates to intolerance of uncertainty and behavioral avoidance in the pathway from GAD to MDD.

In the present study, the indirect effect of stress reactivity in the relationship between MDD and future GAD severity was not significant after controlling for baseline GAD. This finding may suggest that stress reactivity had a stronger association with GAD than MDD, considering that stress reactivity mediated the link in the reverse pathway (i.e., GAD to MDD) even after controlling for baseline MDD. Indeed, etiological and maintenance conceptualizations have often emphasized heightened

Table 3
Mediation model of T1 MDD predicting T3 GAD via T2 Stress Reactivity, controlling for T1 GAD.

	Estimate	95 % CI	Cohen's *d*
Regressions			
(MDD)$_{[T1]}$ ➔ (GAD)$_{[T3]}$	0.525*	[0.103, 0.947]	0.402
(MDD)$_{[T1]}$ ➔ (SR)$_{[T2]}$	0.466*	[0.045, 0.886]	0.358
(SR)$_{[T2]}$ ➔ (GAD)$_{[T3]}$	0.197***	[0.076, 0.318]	0.527
(GAD)$_{[T1]}$ ➔ (GAD)$_{[T3]}$	0.042***	[0.030, 0.055]	1.083
Covariances			
(GAD)$_{[T1]}$ ~~ (MDD)$_{[T1]}$	0.785***	[0.628, 0.943]	0.699
Factor loadings			
T1 MDD 1	1.000***	[1.000, 1.000]	–
T1 MDD 2	0.429***	[0.381, 0.477]	2.907
T1 MDD 3	0.759***	[0.646, 0.873]	2.164
T1 MDD 4	0.981***	[0.906, 1.056]	4.235
T1 MDD 5	0.819***	[0.718, 0.920]	2.619
T1 MDD 6	0.711***	[0.597, 0.826]	2.010
T3 GAD 1	1.000***	[1.000, 1.000]	–
T3 GAD 2	0.696***	[0.567, 0.825]	1.743
T3 GAD 3	0.870***	[0.714, 1.024]	1.827
T3 GAD 4	0.981***	[0.834, 1.127]	2.165
T3 GAD 5	0.962***	[0.794, 1.130]	1.849
T3 GAD 6	1.015***	[0.844, 1.186]	1.917
T3 GAD 7	1.167***	[1.002, 1.332]	2.284
T3 GAD 8	1.226***	[1.028, 1.424]	2.004
T3 GAD 9	1.181***	[0.978, 1.385]	1.878
T3 GAD 10	1.039***	[0.831, 1.247]	1.612
T2 SR 1	1.000***	[1.000, 1.000]	–
T2 SR 2	0.917***	[0.809, 1.113]	1.446
T2 SR 3	1.106***	[0.915, 1.256]	1.465
Residual variances			
T1 MDD 1	0.005***	[0.002, 0.007]	0.510
T1 MDD 2	0.003***	[0.002, 0.004]	0.898
T1 MDD 3	0.014***	[0.010, 0.018]	1.148
T1 MDD 4	0.005**	[0.002, 0.008]	0.548
T1 MDD 5	0.012***	[0.008, 0.016]	1.018
T1 MDD 6	0.014***	[0.011, 0.018]	1.328
T3 GAD 1	0.475***	[0.381, 0.568]	1.641
T3 GAD 2	0.516***	[0.429, 0.603]	1.911
T3 GAD 3	0.500***	[0.414, 0.585]	1.883
T3 GAD 4	0.670***	[0.552, 0.788]	1.837
T3 GAD 5	0.704***	[0.594, 0.815]	2.059
T3 GAD 6	0.409***	[0.340, 0.479]	1.914
T3 GAD 7	0.378***	[0.303, 0.453]	1.633
T3 GAD 8	0.502***	[0.387, 0.617]	1.410
T3 GAD 9	0.546***	[0.427, 0.666]	1.474
T3 GAD 10	0.301***	[0.638, 0.903]	1.881
T2 SR 1	0.040***	[0.416, 0.657]	1.442
T2 SR 2	0.282***	[0.398, 0.590]	1.657
T2 SR 3	0.380***	[0.200, 0.402]	0.964
Residual variances			
Variance of (MDD)$_{[T1]}$	0.033***	[0.028, 0.038]	2.142
Variance of (GAD)$_{[T3]}$	0.299***	[0.232, 0.366]	1.446
Variance of (SR)$_{[T2]}$	0.381***	[0.292, 0.469]	1.394
Variance of (GAD)$_{[T1]}$	4.997***	[3.659, 4.739]	2.515
Defined parameters			
Indirect effect	0.092	[−0.009, 0.192]	0.296
Total effect	0.616**	[0.187, 1.046]	0.464

Note. CI = confidence interval; GAD = generalized anxiety disorder severity; MDD = major depressive disorder symptom severity; SR = stress reactivity; T1 = time 1; T2 = time 2 (9 years after T1) T3 = time 3 (9 years after T2 and 18 years after T1); CFI = confirmatory fit index; RMSEA = root mean square error of approximation; SRMR = standardized root mean squared residual. Model fit indices: $\chi^2(df = 164) = 302.17$, $p < .001$, CFI = 0.980, RMSEA = 0.033, 95 % CI [0.023, 0.041], SRMR = 0.046.

*** $p < .001$.

** $p < .01$.

* $p < .05$.

reactions to stressors and exaggerated threat responses as critical components of GAD (Dennis-Tiwary et al., 2019; Egan and Dennis-Tiwary, 2018; Newman and Llera, 2011; Newman et al., 2022). Moreover, findings from some studies pointed to a stronger association between stress reactivity and anxiety than depression (Gorka et al., 2017; MacNamara et al., 2016; Steudte-Schmiedgen et al., 2017). Providing another possible explanation for these results, the theory of *emotion context insensitivity* posits that depression can result in blunted stress reactivity to emotional cues (Bylsma, 2021; Bylsma et al., 2008). This model hypothesizes that diminished emotional responsiveness might be protective by reducing motivated activity and preserving energy (Bylsma, 2021; Nesse, 2000; Rottenberg, 2005). Lending support to this theory, results from laboratory-based experiments suggested that depression was associated with reduced reactivity to stressors and other negative stimuli (Bylsma et al., 2008; Rottenberg et al., 2005; Schiweck et al., 2019). Considering these findings, blunted stress reactions due to depression could partially explain why stress reactivity was not a robust mechanism linking baseline MDD and future GAD symptoms in the present study. In contrast, however, ecological momentary assessment studies have demonstrated elevated stress reactivity in individuals with current or remitted depression (Husky et al., 2009; O'Hara et al., 2014; van Winkel et al., 2015; Wichers et al., 2007). These mixed findings suggest that more fine-grained and multi-method research may be needed to elucidate the mechanisms between MDD and future GAD symptoms.

Limitations of the current study merit attention. First, unexamined factors (e.g., genetic predispositions, environmental circumstances) may have influenced our findings. The generalizability of the present findings may also be limited by the MIDUS dataset comprising predominantly white American participants. Consequently, these analyses should be replicated utilizing more culturally diverse samples. Further, because stress reactivity was assessed with a subjective measure, this introduced the possibility of self-report bias. Self-perception of stress reactivity is a unique and essential aspect of this trait (Federenko et al., 2006; Schlotz et al., 2011; Shapero et al., 2016). Nonetheless, future studies could test the effect of stress reactivity in the association between GAD and MDD using multimodal stress reactivity measures (e.g., behavioral/physiological markers; Crosswell and Lockwood, 2020; Cummings et al., 2013; Yoon and Joormann, 2012). Lastly, the CIDI-SF used to measure GAD and MDD was based on the DSM-III-R. Thus, replication using current DSM-5 criteria is warranted. Despite these limitations, the present study had several strengths. Findings added to the few longitudinal studies which have explored the bidirectional relations between anxiety and depression over more than a decade. Further, it contributed to the emerging literature on the processes underlying prospective comorbidity and was the first to examine stress reactivity as a mediator across 18 years. Considering that GAD and MDD often precede and predict each other over long durations (Fichter et al., 2010; Kessler et al., 2008; Moffitt et al., 2007; Neufeld et al., 1999), testing mediation mechanisms across comparable timeframes is essential for improving our understanding of these relationships.

If the results herein were replicated, some clinical implications merit consideration. The results suggest that the efficacy of current treatments for GAD and MDD may be strengthened by an increased focus on targeting stress reactivity, which could reduce the risk of developing subsequent disorders and further dysfunction. CBT approaches for GAD and MDD often address emotional reactivity (Fairholme et al., 2010; Mennin and Fresco, 2010; Newman and Borkovec, 2002; Newman et al., 2011; Öst and Breitholtz, 2000). Nevertheless, a stronger emphasis on managing stress reactions could enhance such treatments. For example, mindfulness-based cognitive therapy improved emotional reactivity to interpersonal stress in individuals with a history of depression (Britton et al., 2012). Further, a recent study found that cognitive reappraisal training decreased stress reactivity in a nonclinical sample of young adults (Rozenman et al., 2020). Incorporating similar interventions into CBT may have clinical utility in improving emotional stress reactions for individuals with or at risk for GAD and MDD.

Role of the funding source

The data used in this publication were made available by the Data

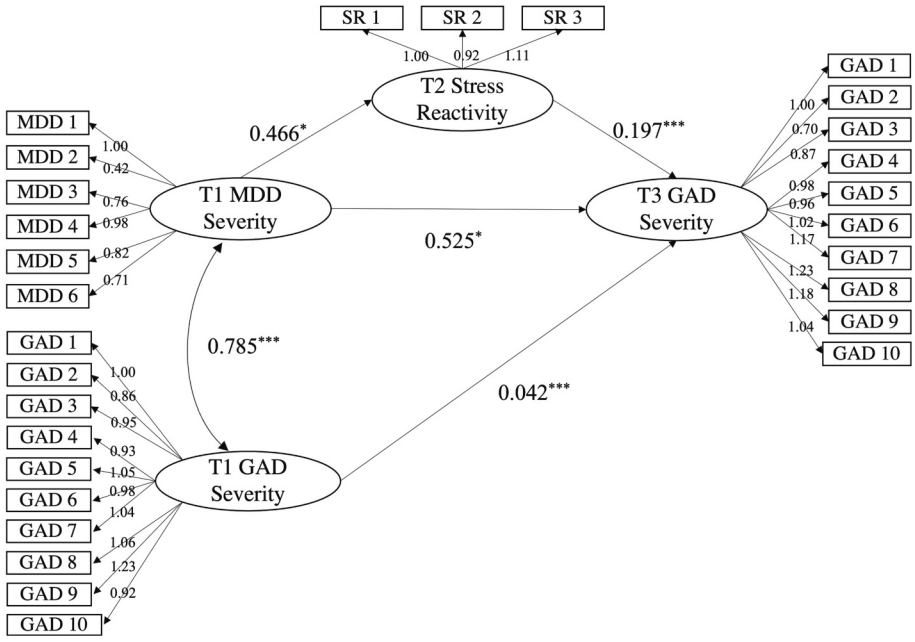

Fig. 2. Mediation model of T1 MDD predicting T3 GAD via T2 stress reactivity.
Note. ***$p < .001$; *$p < .05$.
GAD = generalized anxiety disorder, MDD = major depressive disorder.

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Author contributions

My research team, Dr. Zainal, Dr. Newman, and I, conceived of the presented idea and performed the statistical analyses. Dr. Zainal verified the analytical methods and outputs. Dr. Newman encouraged Dr. Zainal and I to refine on the analyses and supervised the findings of this work. We take full responsibility for the data, the accuracy of analyses and interpretation, as well as conduct of the research. All authors have (1) made substantial contributions to analysis and interpretation of the study and its findings; (2) drafted and revised the article for intellectual content; and (3) gave their final approval of the version to be submitted. The manuscript has been read and approved by all authors.

Conflict of interest

None of the authors, Kathryn E. Barber, Nur Hani Zainal, and Michelle Gayle Newman, have any conflicts to disclose. We do not have any financial relationships (regardless of amount of compensation) with any entity, grants, personal fees, non-financial support, or royalties, and neither have any patents, whether planned, pending or issued, broadly relevant to the work. We confirm that there no other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing, what we wrote in the submitted work.

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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.2023.01.041.

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