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Interactions of Chronic Stress Exposure and Stress Appraisal on Vascular Endothelial Function Among Young Adults

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Abstract

Objective: We investigated the associations of ongoing, chronic stress exposure and stress appraisal on vascular endothelial function (VEF) in young adults.

Methods: In 72 healthy young adults (74% female; age = 25±1 y), we assessed chronic stress exposure and appraisal with a measure that quantified chronic stress exposure and chronic stress appraisal related to 8 specific stressors over the last year. Participants completed the perceived stress scale (PSS) as a measure of global, proximal stress appraisal. VEF was assessed using the brachial artery flow mediated dilation technique. We examined relations among ongoing, chronic stress exposure and stress appraisal versus VEF adjusted for age and sex, and then assessed whether stress appraisal moderated the effect of chronic stress exposure on VEF.

Results: Chronic stress exposure ($\beta=-0.24$, $p=.045$), but not chronic stress appraisal ($\beta=0.07$, $p=.56$) or perceived stress ($\beta=-0.20$, $p=.11$), was related to VEF. Perceived stress ($p=.046$), but not chronic stress appraisal ($p=.54$), moderated the association between chronic stress exposure and VEF. The effect of chronic stress exposure on VEF ceased to be significant at a PSS score of ~22. Subsequent exploratory stratified analysis indicated that those with PSS ≥ 22 had increased exposure to adverse childhood experiences ($+1.6\pm 0.6$, $p=.01$), greater depressive symptoms ($+10.2\pm 2.7$, $p<.001$), and reduced psychological resilience (-7.6 ± 3.5 , $p=.036$).

Conclusions: Chronic stress exposure significantly predicts impaired VEF among young adults. Further, this relation is influenced by proximal perceived stress, such that the association of chronic stress exposure on VEF may be obscured at high levels of proximal perceived stress.

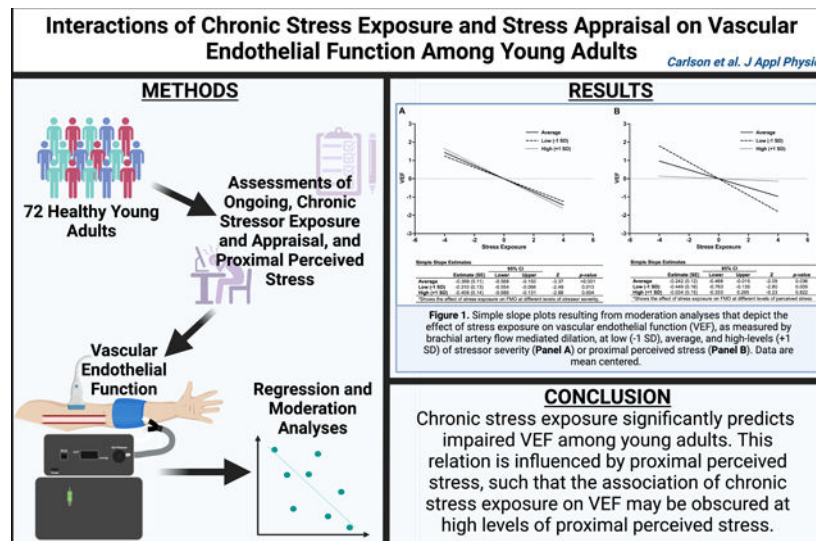
New and Noteworthy: Our findings indicate that ongoing chronic stress exposure over the last year is significantly associated with reduced vascular endothelial function among apparently healthy young adults. Our data provide important insights into the interplay of chronic stress

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exposure versus proximal perceived stress and may also support the hypothesis that young adults who are sensitized to stress may be particularly vulnerable to stress-related impairments in vascular endothelial function.

Graphical Abstract



Keywords

psychosocial stress; early life stress; cardiovascular disease; vascular endothelium; vasodilation

Introduction

The lifetime prevalence of cardiovascular disease (CVD) in adults is >50% and has remained the leading cause of death in the United States for a century (1). Whereas a large emphasis has been placed on traditional risk factors for CVD, there is a growing understanding that psychosocial factors such as psychological stress also contribute independently to CVD risk (2–5). For example, a case-control study that included nearly 25,000 adults from 52 countries reported that individuals who experienced an acute myocardial infarction were 1.5 times more likely to report two or more stressful life events related to work, home, family, or finances in the year prior (6). In support of these findings, evidence from a large, prospective cohort study in 118,706 adults living in 21 different low-, middle-, and high-income countries demonstrated that psychosocial stress at work or home, from major life events, or due to finances contributed to a 20–30% increase in CVD, coronary heart disease, and stroke risk even with adjustment for traditional social, behavioral, and clinical risk factors (7). Thus, compelling epidemiological evidence exists to suggest that psychosocial stress exposure independently contributes to CVD risk, and that the magnitude of risk is comparable to that attributed to traditional CVD risk factors (7, 8). There has been an alarming trend of increasing rates of CVD among young adults (9, 10). Given that young adults are currently reporting higher stress levels than older generations (11) and that young adulthood is a period of life where individuals are at heightened risk to

develop stress disorders (12, 13), it is plausible that psychosocial stress may be contributing to these increases in CVD risk.

The acute neural response to psychosocial stressors includes activation of the limbic system and subsequently of the hypothalamic-pituitary-adrenal and sympathetic-adrenal-medullary axes (4, 14). The downstream physiological effects include increased sympathetic nervous system activity and parasympathetic withdrawal, the secretion of stress-related hormones, immune system activation and the production of inflammatory cytokines and prothrombotic factors, and an increase in peripheral resistance (4, 15). Collectively, this response also contributes to transient reductions in endothelial vasodilatory function (16–18). Whereas this acute physiologic response is protective in emergent situations, it is thought that chronic, repeated exposure to psychosocial stressors may result in cumulative, maladaptive effects that include detrimental vascular endothelial sequelae, the promotion of atherosclerotic progression, and ultimately increased CVD risk (16, 19, 20).

The vascular endothelium is a regulatory organ that plays a critical role in maintaining cardiovascular homeostasis (21). Consequently, vascular endothelial dysfunction is a pathophysiological mechanism contributing to the development of atherosclerosis and CVD (21, 22), and is characterized by reduced endothelium-dependent vasodilatory function in conduit arteries. Recent reports have indicated that psychosocial stress is associated with reduced vascular endothelial function (VEF) among young adults (19, 20, 23), perhaps implicating vascular endothelial dysfunction as a pathophysiological link between psychosocial stress exposure and the development of CVD.

In examining the health-related effects of psychosocial stress, two prevailing models include the differential exposure and differential vulnerability hypotheses (24, 25). The differential exposure hypothesis proposes that differential exposure to psychosocial stressors explain group differences in health, including cardiovascular risk (26, 27). The differential vulnerability hypothesis posits that stress appraisal dictates the effect of stress exposure on health, whereby individuals who perceive stressors as more stressful (i.e., greater stress sensitization) are more strongly impacted (25, 28–30). Notably, while these hypotheses are often presented as competing models, they are not necessarily mutually exclusive. Accordingly, evidence from the Midlife in the United States (MIDUS) cohort study indicated that both the total number of naturalistic stressors experienced during eight days of daily life and the affective reactivity to these stressors were predictive of mortality over 20 years of subsequent follow-up, although the association of affective reactivity with mortality was only present among those with a chronic illness (31). Therefore, to better understand the effects of stress exposure versus stress appraisal on cardiovascular health in young adults, we examined the associations of chronic stress exposure, chronic stress appraisal, and proximal perceived stress with VEF measured by the brachial artery flow mediated dilation technique. Our hypothesis was that the degree of exposure to chronic stressors, rather than chronic stress appraisal or proximal perceived stress, would be more strongly and inversely associated with VEF in young adults. We further conceptualized that stress appraisal would moderate the association between stress exposure and VEF.

METHODS

Participants

Seventy-two participants provided written informed consent, were qualified for study participation, and completed experimental procedures in compliance with the study protocol, which included assessments of ongoing stress exposure and stress appraisal and measurement of vascular endothelial function *in vivo*. Characteristics of these participants are included in Table 1. To be eligible for participation, participants must have been between the ages of 18 and 39 y, have had no diagnosed cardiovascular or metabolic disease or sleep disorder, and have had a body mass index less than 40 kg/m². All participants completed a demographic and health history questionnaire to verify eligibility. Females were also asked to provide information regarding typical menstrual cycle regularity and length and/or birth control use. This study was approved by the University of Iowa Institutional Review Board for the protection of human subjects (IRB ID# 202010095, Original approval date 10/18/2020), and this study represents a secondary analysis of this dataset.

General Experimental Considerations

For experimental visits, participants arrived to the laboratory following an 8–10 h overnight fast. Participants were also instructed to abstain from caffeine for 24 hours and from alcohol and heavy exercise for 48 hours prior to their study visit. Participants were also asked to try to get a full, restful night of sleep the night prior to their visit, to abstain from taking any medications the morning of their study visit, and to arrive euhydrated. Menstrual cycle phase was not controlled based on meta-analytic evidence indicating that menstrual cycle phase does not significantly influence VEF when measured using the FMD technique in accordance with FMD assessment guidelines (32). However, approximate day of menstrual cycle (counted as days from the start of the last menstruation) was documented on the day of the study visit for female participants.

Vascular Endothelial Function

Vascular endothelial function was assessed via the brachial artery flow mediated dilation technique in accordance with current guidelines (33) and as described previously by our team (34, 35). In brief, participants laid supine on a padded medical examination table in a darkened, quiet, temperature controlled (20–22°C) room for 10–15 minutes. The left arm was then extended laterally and supported, and a segmental cuff (TMC7, Hokanson) was placed two inches distal of the medial epicondyle of the humerus. A 12-MHz linear array transducer and high-resolution ultrasound (12L-RS and LOGIQ P9 R3, GE Healthcare, USA) were used to visualize the brachial artery 2–4 cm proximal to the antecubital fold and to measure blood flow using duplex ultrasonography. Blood flow velocity was collected using an insonation angle of 60° to the longitudinal axis of the vessel with a centered, maximized sample volume. Following 1 min of baseline recording, the segmental cuff was inflated to 230–240 mmHg on the forearm (SC5D, Hokanson) with a rapid cuff inflation system (E20, Hokanson) for 5 min, before being instantaneously deflated to induce an increase in blood flow and subsequently in artery diameter. Imaging and recording continued for an additional 3 minutes post-cuff deflation. Throughout the test, a high-definition screen capture device (AV.io HD, Epiphan Systems) was used to continuously record the ultrasound

screen and semi-automated continuous wall-tracking software (FMD Studio) was used to determine FMD as the peak change (%) in artery diameter post-cuff deflation from baseline. Because FMD is dependent on post-occlusion shear rate (SR), we also determined the SR area under the curve (AUC) up to maximal arterial dilation and subsequently report FMD values normalized to SR AUC. Coefficients of variation for brachial artery baseline diameter, diameter change, and relative FMD in our laboratory are 2.6, 3.9, and 5.3% (20).

Ongoing Stress and Stress Appraisal

Ongoing, chronic stress exposure was assessed via a questionnaire that asked participants to report events that were ongoing or recurring stressors for at least the last 12 months. Thus, participants could include stressors that began more than 12 months prior (e.g., 2 years ago) but had to also be present in the past 12 months (i.e., ongoing) to be endorsed. Participants reported if they had experienced: 1) ongoing health problems (in yourself), 2) physical or emotional problems (in a significant other or child), 3) problems with alcohol or drug use in a family member, 4) trouble with a boss or conditions at work, 5) financial strain, 6) housing problems, 7) problems in a close relationship, and/or 8) helping at least one sick/limited/frail family member or friend on a regular basis (30, 36). The cumulative number of ongoing chronic stressors each participant experienced was used as the indicator of ongoing, chronic stress exposure. For each chronic stressor to which participants were exposed, participants also rated the degree to which the stressor was upsetting at the time of the stressor occurrence using a 3-point Likert scale, where: 1 = *it was not upsetting*, 2 = *it was somewhat upsetting*, and 3 = *it was very upsetting* (30, 36). The average stressor severity was used as the primary indicator of chronic stress appraisal. As a secondary indicator of proximal stress appraisal in this study, participants also completed the 10-item Perceived Stress Scale (PSS-10) (37). The PSS-10 specifically assesses perceived stress in the past month, providing a possible score of 0–40, where 0 indicates no perceived stress. The PSS was included as a general (e.g., non-specific to any one stressor) and more proximal indicator of stress appraisal that has also been shown to be relatively stable over time (38). This decision was made with the assumption that appraisal of a specific stressor may not reflect global stress appraisal, which could also interact with chronic stress exposure to influence cardiovascular health. PSS scores were not available for 8 participants; therefore, for analyses reliant on PSS scores the sample size was $n = 64$.

Potential Stress Sensitizing Exposures and Characteristics

We identified three factors in our data set that have previously been put forward as exposures or factors that modulate stress sensitization: cumulative exposure to adverse childhood experiences, depressive symptoms, and psychological resilience (19, 39–41). Adverse childhood experiences were assessed using the 10-item ACE questionnaire, from which a multiplicity of exposure score was obtained where higher scores indicate exposure to more ACEs (20, 42). Depressive symptoms were measured using the 20-item Center for Epidemiological Studies-Depression (CES-D) scale, where higher scores indicate greater depressive symptoms (43, 44). Finally, psychological resilience was assessed using the Connor-Davidson Resilience Scale (CD-RISC), with higher scores indicating greater resilience (45).

Statistical Analyses

Data are presented as mean ($\pm$ SE) or median [IQR]. Exploratory analyses confirmed that VEF was not dependent on menstrual cycle day in females ($p = 0.72$), or on antidepressant ($p = 0.27$) or anxiolytic ($p = 0.80$) medication use in the cohort. The effect of chronic stressor exposure on VEF was also not dependent on antidepressant or anxiolytic medication use. Thus, we first conducted multiple linear regression analyses to examine the effect of stress exposure, stressor severity, and perceived stress on VEF, partialled for age and sex. To better understand whether effects on VEF preceded or were concomitant with effects on blood pressure, post-hoc exploratory analyses were also performed to examine the effect of stress exposure, stressor severity, and perceived stress on systolic and diastolic blood pressure, controlling for age and sex. Bivariate normality was checked by visualizing Q-Q residual plots. Next, moderation analyses (medmod package, jamovi, v. 2.4.14.0; “The jamovi project”) were conducted where chronic stress exposure and VEF were the independent and dependent variables, respectively, and stress appraisal was included as the moderator. Data were mean centered, and SEs for moderation analyses were estimated using the standard method. For each analysis, separate models were run where chronic stressor appraisal or proximal perceived stress scores were included as the measure of stress appraisal. Where a significant moderation effect was observed, we then performed the Johnson-Neyman technique using CAHOST to determine a critical value at which the moderation effect of stress exposure on VEF ceased to be significant (46). In a subsequent post-hoc analysis, we stratified participants based on this critical value to test for the existence of group differences in the three hypothesized exposures or characteristics of interest that may serve to sensitize individuals to stress exposure, which included adverse childhood experiences, depressive symptoms, and psychological resilience. These differences were tested using independent samples t-tests and mean difference $\pm$ SE scores are presented in text. For all analyses, α was set at 0.05.

Transparency and Openness

In this article, we report our sample size, all data exclusions, all manipulations, and all measures that were included in this analysis, which primarily represented *blinded ex post* analyses. After completing the analyses examining our primary hypotheses, we completed an exploratory analysis to test for the existence of differences in the three hypothesized exposures or characteristics of interest that may serve to sensitize individuals to stress exposure. This analysis was completed after the initial *blinded ex post* analyses, but was also blinded and reported in full transparency. All data are available at <https://doi.org/10.7910/DVN/FXQU44>. Data were analyzed using open access statistical programs/packages (47) or worksheets (46), as described in the statistical analysis section.

RESULTS

Individual Relations Among Chronic Stress Exposure, Stress Appraisal, and VEF

The average chronic stress exposure in our sample was 2.9 ± 0.2 (range: 0–7) stressors, the average rated chronic stressor severity was 1.8 ± 0.1 (range: 0–3), and the average proximal perceived stress score was 21 ± 0.4 (range: 15–33). After adjustment for age and sex, greater chronic stress exposure was associated with lower VEF ($\beta = -0.24$; $p = .045$). However,

neither chronic stressor severity ($\beta = 0.07$; $p = .56$) nor proximal perceived stress ($\beta = -0.20$; $p = .11$) was associated with VEF (Table 2).

Exploratory Analysis of Relations Among Chronic Stress Exposure, Stress Appraisal, and Blood Pressure

Niether chronic stress exposure nor chronic stressor severity were associated with brachial systolic ($r = 0.07-0.08$; $p \geq .49$) or diastolic ($r = 0.01-0.10$; $p \geq .42$) blood pressure after partialling for age and sex. However, proximal perceived stress was related to brachial systolic blood pressure ($r = 0.25$; $p = .047$), but was not significantly related to diastolic blood pressure ($r = 0.24$; $p = .06$).

Moderation Analysis: Interaction of Stress Exposure with Stress Appraisal on VEF

Average chronic stressor severity did not moderate the effect of chronic stress exposure on VEF, but proximal perceived stress did (Table 3). Thus, whereas chronic stress exposure was inversely associated with VEF at all levels of chronic stressor severity (Figure 1A), chronic stress exposure was inversely associated with VEF at low and average, but not high levels of proximal perceived stress (Figures 1B and 2B). Results from the Johnson-Neyman technique are displayed in Figure 2A, which indicated that the effect of chronic stress exposure on VEF ceased to be significant at a PSS score of 21.68.

Exploratory Stratification Analyses: Potential Stress Sensitizing Exposures and Characteristics

When compared to individuals for whom the association of cumulative chronic stress exposure on VEF was significant, individuals for whom this association was not significant (i.e., PSS scores ≥ 22) reported greater exposure to adverse childhood experiences ($+1.6 \pm 0.6$, $p = .011$), greater depressive symptoms ($+10.2 \pm 2.7$, $p < .001$), and reduced psychological resilience (-7.6 ± 3.5 , $p = .036$) (Figures 3A–C).

DISCUSSION

This is among the first studies to assess the effects of chronic, ongoing naturalistic stress on conduit artery VEF, inclusive of cumulative chronic stressor exposure and chronic and proximal stress appraisal in young adults. As hypothesized, those who reported greater cumulative exposure to chronic stressors also exhibited reduced VEF. Interestingly, the present findings showed that neither appraisal of chronic stressors, nor perceived stress in the past month were significantly associated with VEF in our sample. While chronic stress appraisal did not modify the relation between chronic stress exposure and VEF, proximal perceived stress did. Specifically, the relation between chronic stress exposure and VEF was significant at low and average levels of proximal perceived stress, whereas there was no relation at high levels of proximal perceived stress. We then determined that the association of chronic stress exposure on VEF was significant only at PSS scores less than 22. Notably, individuals with PSS scores ≥ 22 had greater exposure to factors that may sensitize individuals to stress than individuals with PSS scores < 22 , including greater adverse childhood experiences and depressive symptoms, and lower psychological resilience. Thus, overall, our results demonstrated that exposure to common, chronic psychosocial stressors

was most strongly predictive of VEF in young adults, and that this association is dependent upon proximal perceived stress.

Our findings indicate that even among healthy, young adults with no existing cardiovascular or metabolic disease, exposure to chronic stressors is associated with reduced VEF but not brachial blood pressure, which aligns with prior evidence linking chronic naturalistic stressor exposure to the development and progression of disease (48, 49) and portends risk for the future development of CVD. However, neither chronic stress appraisal nor proximal perceived stress were individually associated with VEF in our study. Similarly, Greaney and colleagues (50) reported that the number of exposures to common daily stressors is positively associated with microvascular vasoconstrictor responsiveness to noradrenergic stimulation in young adults. Also consistent with our findings, Greaney et al. (50) reported that perceived stressor severity was not significantly associated with vascular function. These findings also agree with data from the MIDUS study, which indicated that greater cumulative stressor exposure in mid-life was linked with increased mortality risk during 20 years of follow-up, whereas negative affective reactivity to naturalistic stressors only predicted increased mortality among individuals with a chronic health condition (31). Therefore, our findings lend support to reduced VEF as an important pathophysiological mechanism linking chronic stress exposure with future CVD and, potentially, mortality risk. These findings also lend credence to the differential exposure hypothesis, indicating that increasing exposure to chronic stressors is sufficient to promote reduced VEF.

Conceptually, exposure to and appraisal of stressors are not independent phenomena, and instead stressor appraisal may modify the degree to which stressor exposure negatively impacts health. Indeed, whereas repeated activation of the physiological stress systems would be expected to adversely impact cardiovascular health, it is reasonable to suspect that this may be further exacerbated by heightened reactivity among individuals who perceive the stressor(s) as more upsetting. Thus, our study takes an important step by building on prior studies to test the hypothesis that stress appraisal moderates the association of exposure to chronic naturalistic stressors with reduced VEF. In partial accordance with our hypothesis, proximal perceived stress was a significant moderator (Figure 1B), but appraisal of the chronic stressors themselves was not (Figure 1A). Interestingly, our data indicate that while stress exposure magnitude was significantly and inversely associated with VEF at low ($-1SD$) and moderate (average) levels of proximal perceived stress for our sample, it was not among individuals who reported high ($+1SD$) levels of proximal perceived stress. Examination of the simple slopes (Figure 2B) further suggests that individuals with high perceived stress have lower VEF even at low chronic stress exposure. Therefore, our findings indicate that the association of chronic stressor exposure with reduced VEF is not dependent on appraisal of the chronic stressors but is dependent on proximal perceived stress.

As stated, when individuals reported greater proximal perceived stress, VEF was less impacted by the magnitude of exposure to common, chronic psychosocial stressors. Although seemingly counterintuitive, these findings could be explained by increased stress sensitization among those with high levels of proximal perceived stress, such that individuals are *more* impacted by chronic stressors and perceive high levels of stress at low levels of

chronic stress exposure (51). For example, for an individual who is sensitized to stress, low exposure to chronic stress will result in higher proximal perceived stress, whereas for someone who is less sensitized to stress, high exposure to chronic stress will be required to result in high proximal perceived stress (52). This model has been used previously to identify groups who may be more prone to experience psychopathology in response to psychosocial stress exposure (53). For example, individuals with a history of adverse childhood experiences have been shown to be sensitized to subsequent proximal stress, increasing their risk of later psychopathology (51). To further test this hypothesis, we performed the Johnson-Neyman technique to determine the level of proximal perceived stress at which the association of chronic stress exposure magnitude with VEF ceased to be significant (46). Our analysis indicated that the critical PSS score in our sample was approximately 22. Thus, we stratified our sample into two groups based on PSS scores below and equal to or above this critical value and performed comparisons examining factors that have been previously linked to stress sensitization or resilience (19, 39–41). Our findings confirmed that individuals with a $PSS \geq 22$ indeed had greater exposure to adverse childhood experiences, greater depressive symptoms, and lower psychological resilience (Figure 3A–C).

While our findings appear to support an effect of stress sensitization in association with prior early life adversity, depressive symptoms, and low psychological resilience, there are several very important considerations that must be taken into account. First, there were no differences observed in chronic stress appraisal among individuals below and equal to the critical PSS score. However, stress sensitization may best be defined by the coupling of stress and affect (i.e., the affective response to stress exposure) (54) which was not assessed in this study, and thus the lack of difference in chronic stress appraisal also does not preclude an effect of stress sensitization. It is also important to consider that proximal stress appraisal as measured in this study was not directly resultant from the chronic stress exposures assessed and, when also considered against the potential temporal discordance of chronic stressor exposure and proximal perceived stress, it is difficult to ascertain with certainty the role of stress sensitization. However, it is also worth considering that the PSS has also been shown to reflect, in part, a stable characteristic describing how an individual perceives stressful life circumstances (38). Regardless, these findings raise several interesting hypotheses that will require future work with careful determination of temporality and more wholistic examination of stress sensitization, including assessments of affective responsiveness.

It should also be considered that our observance of differences in adverse childhood experiences, greater depressive symptoms, and lower psychological resilience are a statistical artifact as a result of expected linear relations among these variables. Thus, an alternative and simpler explanation is that these findings reflect interacting negative impacts of both proximal stress appraisal and chronic stress exposure on VEF, where high perceived stress proximal to the experimental visit superceded, and thus obscured, the effect of chronic stress exposure on VEF (55). Consequently, the effect of chronic stress exposure on VEF was apparent at low, but not high PSS scores. This finding has important implications for rigor, reproducibility, and study design, indicating that careful measurement of acute (proximal) stress is a necessary consideration when attempting to precisely

delineate the effect(s) of chronic stress exposure on VEF. Finally, while it is beyond the scope of this study, it will be important for future studies to better understand how and if factors such as adverse childhood experience exposure, depression, and psychological coping interact in these associations and how this translates to cardiovascular risk, with the goal of identifying interventions that ultimately promote cardiovascular resilience among susceptible populations.

There are several strengths, limitations, and considerations to note when considering our findings. First, while our participant sample is representative of the population of the local region in which the data was collected, White/non-Hispanic adults are overrepresented in our sample relative to national ethno-racial demographics. Second, whereas chronic stress exposure and appraisal were the focus of this study, rumination and affective (emotional) responsiveness have been previously associated with reduced endothelial function, such as in those with major depressive disorder (19), and may not necessarily be dependent on stressor severity. Future studies should include measures of affective responsiveness to elucidate whether these modify the effect of stress exposure on VEF. Additionally, both chronic and proximal stress were assessed via retrospective self-report, which increases risk of response bias (i.e., artificially high levels of stress may have been reported if the day questions were answered was particularly stressful). To partially circumvent this possibility, stress was assessed via multiple modalities, such that the measurement of stress and subsequent conclusions were not entirely dependent on one self-report measure. Furthermore, the scales used to assess stress were implemented at least one week prior to the experimental visit where VEF was assessed to better isolate the effect of chronic versus acute stress. Future studies using a prospective design and daily or semi-daily (e.g., ecological momentary assessments) surveys of naturalistic stressors and stress appraisal would be advantageous. Of consideration, the range of reported perceived stress scores in our sample corresponds qualitatively with “moderate” (e.g., PSS scores of 14–26; $n=60$) and “high” (e.g., PSS scores of 27–40; $n=5$) perceived stress levels. Thus, in our moderation analysis, the association of chronic stress exposure with VEF, as measured by FMD, at low perceived stress (-1 SD) is in fact at moderate (~ 18) perceived stress. However, it is important to consider that these results are representative of young adults, and that this may in fact reflect typical stress levels in this population, particularly in contemporary society (56).

Given that young adulthood is a period of life where individuals are at heightened risk to develop stress disorders (12, 13) and the alarming recent increases in CVD risk among young adults (9, 10), our data provide important insight linking chronic stress with CVD risk among this population. More specifically, our findings indicate that the cumulative magnitude of chronic stress exposure is significantly associated with reduced VEF among otherwise healthy young adults. While chronic stressor severity and proximal perceived stress did not directly associate with VEF, proximal perceived stress did moderate the effect of chronic stress exposure on VEF. Therefore, our data highlight reduced VEF as an important pathophysiological mechanism linking chronic stress exposure with CVD risk in young adults, and indicate that the degree to which chronic stress is associated with reduced VEF is dependent on proximal stress appraisal. Accordingly, our findings emphasize that measures of proximal stress are necessary to fully understand the influence of chronic stress exposure on cardiovascular health. Our findings may also suggest that factors such as

adverse childhood experiences, depression, and psychological resilience may play a role in stress-exposure related cardiovascular risk, although prospective longitudinal studies will be critical to better understand how these factors interact to ultimately promote cardiovascular risk or resilience.

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REFERENCES

1. Wilkins JT, Ning H, Berry J, Zhao L, Dyer AR, **and** Lloyd-Jones DM. Lifetime risk and years lived free of total cardiovascular disease. *JAMA* 308: 1795–1801, 2012. [PubMed: 23117780]
2. Neylon A, Canniffe C, Anand S, Kreatsoulas C, Blake GJ, Sugrue D, **and** McGorrian C. A global perspective on psychosocial risk factors for cardiovascular disease. *Prog Cardiovasc Dis* 55: 574–581, 2013. [PubMed: 23621967]
3. Lloyd-Jones DM, Allen NB, Anderson CAM, Black T, Brewer LC, Foraker RE, Grandner MA, Lavretsky H, Perak AM, Sharma G, Rosamond W, **and** American Heart A. Life's Essential 8: Updating and Enhancing the American Heart Association's Construct of Cardiovascular Health: A Presidential Advisory From the American Heart Association. *Circulation* 146: e18–e43, 2022. [PubMed: 35766027]
4. Rogers EM, Banks NF, **and** Jenkins NDM. The effects of sleep disruption on metabolism, hunger, and satiety, and the influence of psychosocial stress and exercise: A narrative review. *Diabetes Metab Res Rev* 40: e3667, 2024. [PubMed: 37269143]
5. Levine GN, Cohen BE, Commodore-Mensah Y, Fleury J, Huffman JC, Khalid U, Labarthe DR, Lavretsky H, Michos ED, Spatz ES, **and** Kubzansky LD. Psychological Health, Well-Being, and the Mind-Heart-Body Connection: A Scientific Statement From the American Heart Association. *Circulation* 143: e763–e783, 2021. [PubMed: 33486973]
6. Rosengren A, Hawken S, Ounpuu S, Sliwa K, Zubaid M, Almahmeed WA, Blackett KN, Sitthiamorn C, Sato H, Yusuf S, **and** investigators I. Association of psychosocial risk factors with risk of acute myocardial infarction in 11119 cases and 13648 controls from 52 countries (the INTERHEART study): case-control study. *Lancet* 364: 953–962, 2004. [PubMed: 15364186]
7. Santosa A, Rosengren A, Ramasundarahettige C, Rangarajan S, Gulec S, Chifamba J, Lear SA, Poirier P, Yeates KE, Yusuf R, Orlandini A, Weida L, Sidong L, Yibing Z, Mohan V, Kaur M, Zatonska K, Ismail N, Lopez-Jaramillo P, Iqbal R, Palileo-Villanueva LM, Yusufali AH, AlHabib KF, **and** Yusuf S. Psychosocial Risk Factors and Cardiovascular Disease and Death in a Population-Based Cohort From 21 Low-, Middle-, and High-Income Countries. *JAMA Netw Open* 4: e2138920, 2021.
8. Osborne MT, Shin LM, Mehta NN, Pitman RK, Fayad ZA, **and** Tawakol A. Disentangling the Links Between Psychosocial Stress and Cardiovascular Disease. *Circ Cardiovasc Imaging* 13: e010931, 2020.
9. Aggarwal R, Yeh RW, Joynt Maddox KE, **and** Wadhera RK. Cardiovascular Risk Factor Prevalence, Treatment, and Control in US Adults Aged 20 to 44 Years, 2009 to March 2020. *JAMA* 329: 899–909, 2023.
10. Andersson C, **and** Vasan RS. Epidemiology of cardiovascular disease in young individuals. *Nat Rev Cardiol* 15: 230–240, 2018. [PubMed: 29022571]
11. Association AP. Stress in America: A Nation Recovering from Collective Trauma 2023.

12. Varma P, Junge M, Meaklim H, **and** Jackson ML. Younger people are more vulnerable to stress, anxiety and depression during COVID-19 pandemic: A global cross-sectional survey. *Prog Neuropsychopharmacol Biol Psychiatry* 109: 110236, 2021. [PubMed: 33373680]
13. LeBlanc NJ, Brown M, **and** Henin A. Anxiety Disorders in Emerging Adulthood. In: *Clinical Handbook of Anxiety Disorders: From Theory to Practice*, edited by Bui E, Charney ME, and Baker AW. Cham: Springer International Publishing, 2020, p. 157–173.
14. Russell G, **and** Lightman S. The human stress response. *Nat Rev Endocrinol* 15: 525–534, 2019. [PubMed: 31249398]
15. Kivimaki M, Bartolomucci A, **and** Kawachi I. The multiple roles of life stress in metabolic disorders. *Nat Rev Endocrinol* 19: 10–27, 2023. [PubMed: 36224493]
16. Poitras VJ, **and** Pyke KE. The impact of acute mental stress on vascular endothelial function: evidence, mechanisms and importance. *Int J Psychophysiol* 88: 124–135, 2013. [PubMed: 23562766]
17. Ghiadoni L, Donald AE, Cropley M, Mullen MJ, Oakley G, Taylor M, O'Connor G, Betteridge J, Klein N, Steptoe A, **and** Deanfield JE. Mental stress induces transient endothelial dysfunction in humans. *Circulation* 102: 2473–2478, 2000. [PubMed: 11076819]
18. Strawn WB, Bondjers G, Kaplan JR, Manuck SB, Schwenke DC, Hansson GK, Shively CA, **and** Clarkson TB. Endothelial dysfunction in response to psychosocial stress in monkeys. *Circ Res* 68: 1270–1279, 1991. [PubMed: 2018991]
19. Greaney JL, Koffer RE, Saunders EFH, Almeida DM, **and** Alexander LM. Self-Reported Everyday Psychosocial Stressors Are Associated With Greater Impairments in Endothelial Function in Young Adults With Major Depressive Disorder. *J Am Heart Assoc* 8: e010825, 2019.
20. Jenkins NDM, Rogers EM, Banks NF, Tomko PM, Sciarillo CM, Emerson SR, Taylor A, **and** Teague TK. Childhood psychosocial stress is linked with impaired vascular endothelial function, lower SIRT1, and oxidative stress in young adulthood. *Am J Physiol Heart Circ Physiol* 321: H532–H541, 2021. [PubMed: 34328346]
21. Rubanyi GM. The role of endothelium in cardiovascular homeostasis and diseases. *J Cardiovasc Pharmacol* 22 Suppl 4: S1–14, 1993.
22. Sitia S, Tomasoni L, Atzeni F, Ambrosio G, Cordiano C, Catapano A, Tramontana S, Perticone F, Naccarato P, Camici P, Picano E, Cortigiani L, Bevilacqua M, Milazzo L, Cusi D, Barlassina C, Sarzi-Puttini P, **and** Turiel M. From endothelial dysfunction to atherosclerosis. *Autoimmun Rev* 9: 830–834, 2010. [PubMed: 20678595]
23. Rodriguez-Miguel P, Looney J, Blackburn M, Thomas J, Pollock JS, **and** Harris RA. The Link Between Childhood Adversity and Cardiovascular Disease Risk: Role of Cerebral and Systemic Vasculature. *Function (Oxf)* 3: zqac029, 2022.
24. McDonough P, **and** Walters V. Gender and health: reassessing patterns and explanations. *Soc Sci Med* 52: 547–559, 2001. [PubMed: 11206652]
25. Vanroelen C, Levecque K, **and** Louckx F. Differential exposure and differential vulnerability as counteracting forces linking the psychosocial work environment to socioeconomic health differences. *J Epidemiol Community Health* 64: 866–873, 2010. [PubMed: 19822559]
26. Joost Oude G, Tanja AJH, Pauline WJ, Nil H, Buil JM, Pol ACvL, and Frank JvL. Social inequalities in child development: the role of differential exposure and susceptibility to stressful family conditions. *Journal of Epidemiology and Community Health* 77: 74, 2023. [PubMed: 36428086]
27. Suglia SF, Appleton AA, Bleil ME, Campo RA, Dube SR, Fagundes CP, Heard-Garris NJ, Johnson SB, Slopen N, Stoney CM, **and** Watamura SE. Timing, duration, and differential susceptibility to early life adversities and cardiovascular disease risk across the lifespan: Implications for future research. *Preventive Medicine* 153: 106736, 2021.
28. Alhurani AS, Dekker R, Ahmad M, Miller J, Yousef KM, Abdulqader B, Salami I, Lennie TA, Randall DC, **and** Moser DK. Stress, cognitive appraisal, coping, and event free survival in patients with heart failure. *Heart Lung* 47: 205–210, 2018. [PubMed: 29627073]
29. McEwen BS. Protective and damaging effects of stress mediators. *N Engl J Med* 338: 171–179, 1998. [PubMed: 9428819]

30. Brown LL, Abrams LR, Mitchell UA, **and** Ailshire JA. Measuring More Than Exposure: Does Stress Appraisal Matter for Black-White Differences in Anxiety and Depressive Symptoms Among Older Adults? *Innov Aging* 4: igaa040, 2020.
31. Chiang JJ, Turiano NA, Mroczek DK, **and** Miller GE. Affective reactivity to daily stress and 20-year mortality risk in adults with chronic illness: Findings from the National Study of Daily Experiences. *Health Psychol* 37: 170–178, 2018. [PubMed: 29154603]
32. Williams JS, Dunford EC, **and** MacDonald MJ. Impact of the menstrual cycle on peripheral vascular function in premenopausal women: systematic review and meta-analysis. *Am J Physiol Heart Circ Physiol* 319: H1327–H1337, 2020. [PubMed: 33064553]
33. Thijssen DHJ, Bruno RM, van Mil A, Holder SM, Fata F, Greyling A, Zock PL, Taddei S, Deanfield JE, Luscher T, Green DJ, **and** Ghiadoni L. Expert consensus and evidence-based recommendations for the assessment of flow-mediated dilation in humans. *Eur Heart J* 40: 2534–2547, 2019. [PubMed: 31211361]
34. Banks NF, Rogers EM, Berry AC, **and** Jenkins NDM. Progressive iso-inertial resistance exercise promotes more favorable cardiovascular adaptations than traditional resistance exercise in young adults. *Am J Physiol Heart Circ Physiol* 326: H32–H43, 2024. [PubMed: 37889252]
35. Banks NF, Rogers EM, Stanhewicz AE, Whitaker KM, **and** Jenkins NDM. Resistance exercise lowers blood pressure and improves vascular endothelial function in individuals with elevated blood pressure or stage-1 hypertension. *Am J Physiol Heart Circ Physiol* 326: H256–H269, 2024. [PubMed: 37975709]
36. Troxel WM, Matthews KA, Bromberger JT, **and** Sutton-Tyrrell K. Chronic stress burden, discrimination, and subclinical carotid artery disease in African American and Caucasian women. *Health Psychol* 22: 300–309, 2003. [PubMed: 12790258]
37. Cohen S, Kamarck T, **and** Mermelstein R. A Global Measure of Perceived Stress. *Journal of Health and Social Behavior* 24: 385–396, 1983. [PubMed: 6668417]
38. Harris KM, Gaffey AE, Schwartz JE, Krantz DS, **and** Burg MM. The Perceived Stress Scale as a Measure of Stress: Decomposing Score Variance in Longitudinal Behavioral Medicine Studies. *Ann Behav Med* 57: 846–854, 2023. [PubMed: 37084792]
39. Bandoli G, Campbell-Sills L, Kessler RC, Heeringa SG, Nock MK, Rosellini AJ, Sampson NA, Schoenbaum M, Ursano RJ, **and** Stein MB. Childhood adversity, adult stress, and the risk of major depression or generalized anxiety disorder in US soldiers: a test of the stress sensitization hypothesis. *Psychol Med* 47: 2379–2392, 2017. [PubMed: 28443533]
40. Choi KW, Nishimi K, Jha SC, Sampson L, Hahn J, Kang JH, Koenen KC, **and** Kubzansky LD. Pre-pandemic resilience to trauma and mental health outcomes during COVID-19. *Soc Psychiatry Psychiatr Epidemiol* 58: 453–465, 2023. [PubMed: 36169684]
41. Hofgaard LS, Nes RB, **and** Roysamb E. Introducing two types of psychological resilience with partly unique genetic and environmental sources. *Sci Rep* 11: 8624, 2021. [PubMed: 33883571]
42. Felitti VJ, Anda RF, Nordenberg D, Williamson DF, Spitz AM, Edwards V, Koss MP, **and** Marks JS. Relationship of childhood abuse and household dysfunction to many of the leading causes of death in adults. The Adverse Childhood Experiences (ACE) Study. *Am J Prev Med* 14: 245–258, 1998. [PubMed: 9635069]
43. Lewinsohn PM, Seeley JR, Roberts RE, **and** Allen NB. Center for Epidemiologic Studies Depression Scale (CES-D) as a screening instrument for depression among community-residing older adults. *Psychol Aging* 12: 277–287, 1997. [PubMed: 9189988]
44. Radloff LS. The CES-D Scale: A Self-Report Depression Scale for Research in the General Population. *Applied Psychological Measurement* 1: 385–401, 1977.
45. Connor KM, **and** Davidson JR. Development of a new resilience scale: the Connor-Davidson Resilience Scale (CD-RISC). *Depress Anxiety* 18: 76–82, 2003. [PubMed: 12964174]
46. Carden SW, Holtzman NS, **and** Strube MJ. CAHOST: An Excel Workbook for Facilitating the Johnson-Neyman Technique for Two-Way Interactions in Multiple Regression. *Front Psychol* 8: 1293, 2017. [PubMed: 28804471]
47. The jamovi project. 2024.
48. Salleh MR. Life event, stress and illness. *Malays J Med Sci* 15: 9–18, 2008. [PubMed: 22589633]

49. Segerstrom SC, **and** Miller GE. Psychological stress and the human immune system: a meta-analytic study of 30 years of inquiry. *Psychol Bull* 130: 601–630, 2004. [PubMed: 15250815]
50. Greaney JL, Surachman A, Saunders EFH, Alexander LM, **and** Almeida DM. Greater Daily Psychosocial Stress Exposure is Associated With Increased Norepinephrine-Induced Vasoconstriction in Young Adults. *J Am Heart Assoc* 9: e015697, 2020.
51. McLaughlin KA, Conron KJ, Koenen KC, **and** Gilman SE. Childhood adversity, adult stressful life events, and risk of past-year psychiatric disorder: a test of the stress sensitization hypothesis in a population-based sample of adults. *Psychol Med* 40: 1647–1658, 2010. [PubMed: 20018126]
52. Stroud CB. The Stress Sensitization Model. *The Oxford Handbook of Stress and Mental Health* 2018.
53. Stroud CB, Davila J, Hammen C, **and** Vrshek-Schallhorn S. Severe and nonsevere events in first onsets versus recurrences of depression: evidence for stress sensitization. *J Abnorm Psychol* 120: 142–154, 2011. [PubMed: 21171724]
54. Sliwinski MJ, Almeida DM, Smyth J, **and** Stawski RS. Intraindividual change and variability in daily stress processes: findings from two measurement-burst diary studies. *Psychol Aging* 24: 828–840, 2009. [PubMed: 20025399]
55. Shimbo D, Cohen MT, McGoldrick M, Ensari I, Diaz KM, Fu J, Duran AT, Zhao S, Suls JM, Burg MM, **and** Chaplin WF. Translational Research of the Acute Effects of Negative Emotions on Vascular Endothelial Health: Findings From a Randomized Controlled Study. *J Am Heart Assoc* 13: e032698, 2024.
56. van Loon AWG, Creemers HE, Vogelaar S, Saab N, Miers AC, Westenberg PM, **and** Asscher JJ. Trajectories of adolescent perceived stress and symptoms of depression and anxiety during the COVID-19 pandemic. *Sci Rep* 12: 15957, 2022. [PubMed: 36153394]

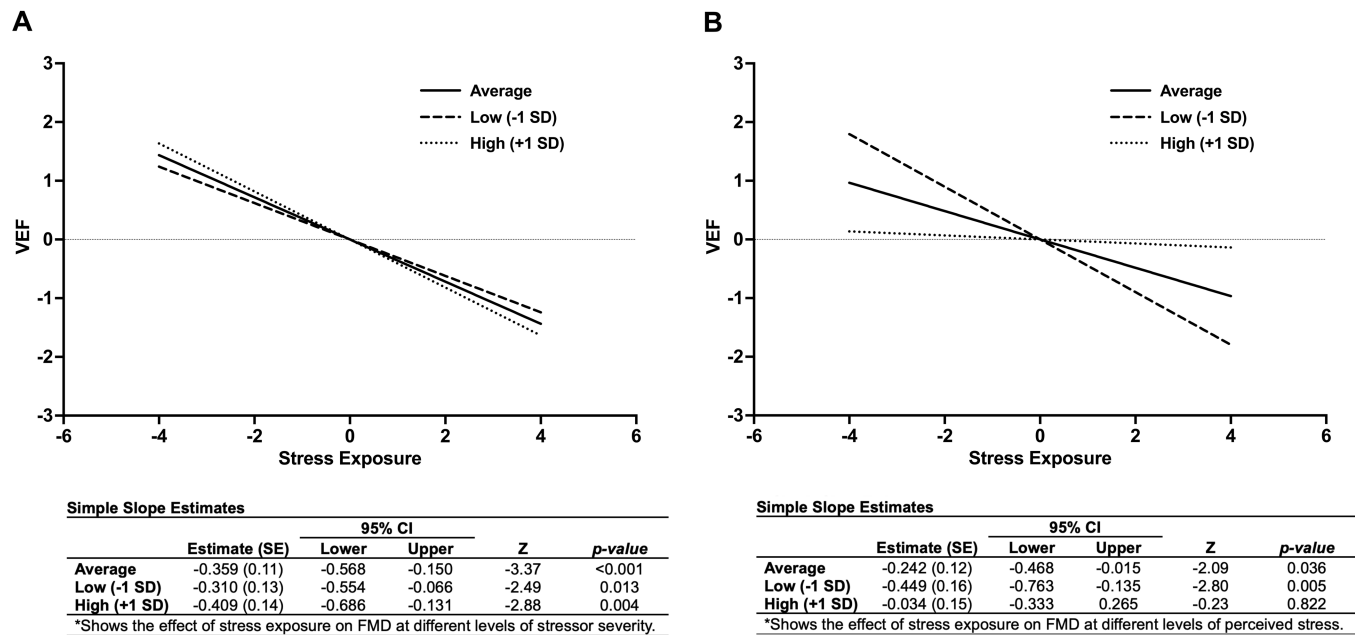


Figure 1. Simple slope plots resulting from moderation analyses that depict the effect of stress exposure on vascular endothelial function (VEF), as measured by brachial artery flow mediated dilation, at low (–1 SD), average, and high-levels (+1 SD) of stressor severity (**Panel A**) or perceived stress (**Panel B**). Data are mean centered.

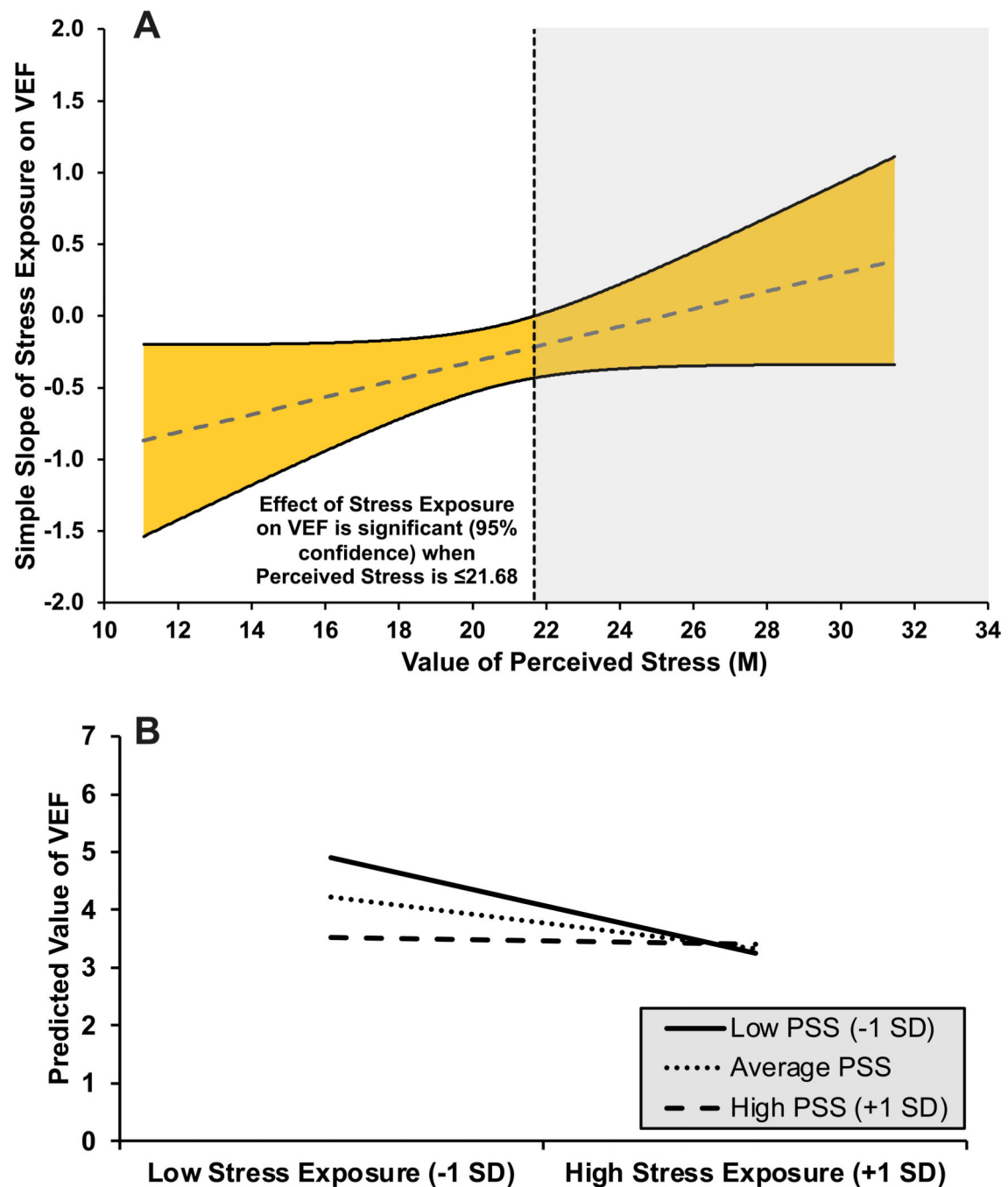


Figure 2.

(Panel A) Plot illustrating the results of the Johnson-Neyman technique to determine the perceived stress score at which the effect of stress exposure on vascular endothelial function (VEF), as measured by brachial artery flow mediated dilation, ceases to be significant, performed using CAHOST (46). The shaded region represents the perceived stress scores at which the effect of stress exposure on VEF was not significant. **(Panel B)** The simple slopes plot demonstrating the interactions among stress exposure (X), perceived stress (M), and VEF (Y).

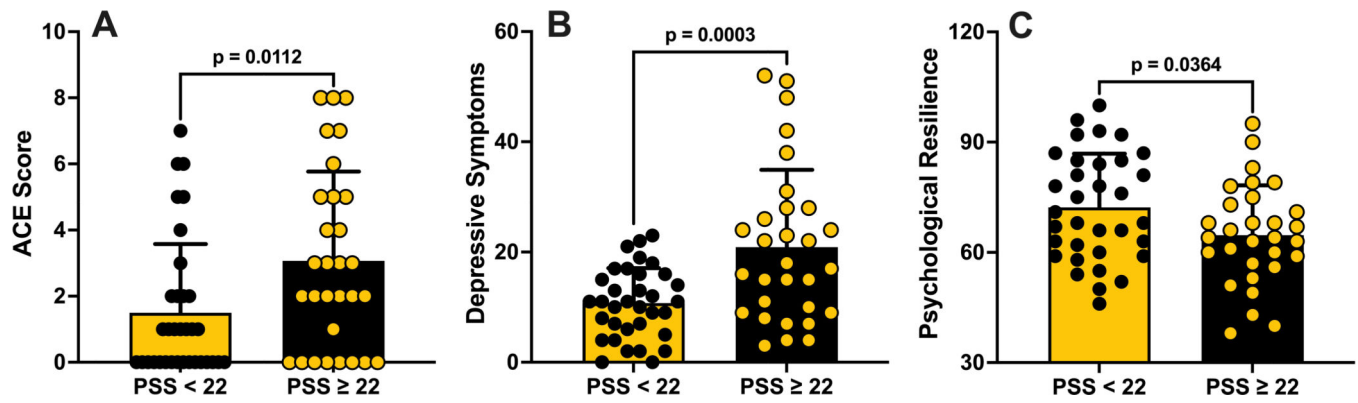


Figure 3.

Comparisons of **(Panel A)** ACE exposure, **(Panel B)** depressive symptoms, and **(Panel C)** psychological resilience among individuals above and below the critical perceived stress value at which the association of stress exposure on VEF ceased to be significant (e.g., PSS = 22).

Table 1.

Participant characteristics in full sample (n = 72).

Characteristic	Mean $\pm$ SE or n (%)
Age (y)	25 $\pm$ 1
Sex (n (%))	
Female	53 (74%)
Male	19 (26%)
Race (n (%))	
White	58 (81%)
Non-White	14 (19%)
Ethnicity (n (%))	
Hispanic-Latino	8 (11%)
Not Hispanic-Latino	64 (89%)
Day of Menstrual Cycle	15 $\pm$ 2
Birth Control Usage (n (%))	18 (25%)
Antidepressant Drug Use (n (%))	14 (19%)
Anxiolytic Drug Use (n (%))	16 (22%)
ACE Score	2.2 $\pm$ 0.3
CESD Score	15.3 $\pm$ 1.5
CD-RISC Score	67.8 $\pm$ 14.4
Height (cm)	169.0 $\pm$ 1.1
Weight (kg)	72.6 $\pm$ 1.7
BMI (kg/m ²)	25.5 $\pm$ 0.6
Heart Rate (bpm)	74 $\pm$ 1
Systolic Blood Pressure (mmHg)	119 $\pm$ 1
Diastolic Blood Pressure (mmHg)	77 $\pm$ 1
Fasting Blood Glucose (mg/dL)	92 $\pm$ 1
Fasting Total Cholesterol (mg/dL)	169 $\pm$ 4
Fasting HDL Cholesterol (mg/dL)	53 $\pm$ 2
Baseline Arterial Diameter (mm)	3.13 $\pm$ 0.05
Peak Arterial Diameter (mm)	3.34 $\pm$ 0.06
Shear Rate AUC	19,453 $\pm$ 978
FMD (%)	6.7 $\pm$ 0.4%
nFMD (%/SR _{AUC})	3.7 $\pm$ 0.2

Abbreviations: ACE, adverse childhood experiences; CESD, center for epidemiologic studies depression; CD-RISC, Connor-Davidson Resilience Scale; BMI, body mass index; AUC, area under the curve; FMD, flow mediated dilation; SR, shear rate

Table 2.

The relations between stress exposure, stressor severity, and perceived stress with VEF, adjusted for age and sex.

Predictor	B ₀ (SE)	B ₁ (SE)	β ₁ (95% CI)	t	p-value
Stress Exposure	4.94 (1.10)	-0.23 (0.11)	-0.24 (-0.45 – -0.005)	-2.04	0.045
Stressor Severity	3.85 (1.25)	0.16 (0.29)	0.07 (-0.40 – 0.74)	0.58	0.56
Perceived Stress	6.91 (1.99)	-0.11 (0.07)	-0.21 (-0.24 – 0.03)	-1.61	0.11

B₀, unstandardized intercept coefficient; B₁, unstandardized predictor coefficient, β₁, standardized predictor coefficient. t and p-values are shown for predictors (B₁).

Table 3.

Moderation effects of stress appraisal on relation between stress exposure and VEF.

Moderation Effect	Effect Estimate (SE)	Z-value	p-value
Stress Exposure × Stressor Severity	−0.07 (0.11)	−0.62	0.54
Stress Exposure × Perceived Stress	0.06 (0.03)	2.00	0.046