

# Daily Stress and Microvascular Dysfunction: The Buffering Effect of Physical Activity

Jody L. Greaney<sup>1</sup>, Ashley M. Darling<sup>1</sup>, Erika F.H. Saunders<sup>2</sup>, and David M. Almeida<sup>3,4</sup>

<sup>1</sup>Department of Kinesiology, The University of Texas at Arlington, Arlington, TX; <sup>2</sup>Department of Psychiatry and Behavioral Health Penn State College of Medicine, Hershey, PA; <sup>3</sup>Department of Human Development and Family Studies, and <sup>4</sup>Center for Healthy Aging, The Pennsylvania State University, University Park, PA

GREANEY, J.L., A.M. DARLING, E.F.H. SAUNDERS, and D.M. ALMEIDA. Daily stress and microvascular dysfunction: the buffering effect of physical activity. *Exerc. Sport Sci. Rev.*, Vol. 51, No. 1, pp. 19–26, 2023. *Although often short-lived, emotional responsiveness to daily stressors (i.e., routine and sometimes unexpected everyday hassles) is associated with increased cardiovascular disease (CVD), morbidity, and mortality. Here, we present the novel hypothesis that a disruption of microvascular homeostasis is a key antecedent. In addition, we postulate that physical activity may mitigate the psychobiological consequences of daily stress, thereby limiting pathophysiological CVD-related sequelae.* **Key Words:** negative affective responsivity, intradermal microdialysis, norepinephrine, sympathetic, vasoconstriction

## Key Points

- In contrast to major life events or chronic stress, myriad common stressful events permeate everyday life, such as the routine challenges and unexpected and episodic hassles that disrupt day-to-day living (e.g., argument with a spouse, malfunctioning computer).
- Although daily stressors are relatively minor, greater emotional responsivity to daily stressor occurrence is linked to increased chronic disease risk.
- Microvascular dysfunction, characterized by both blunted endothelium-dependent dilation and exaggerated sympathetic vasoconstriction, is evident in adults who are more susceptible to daily stress, which may be one underlying mechanism contributing to increased risk of future cardiovascular disease.
- Increased habitual physical activity buffers the emotional responsivity of daily stress and, in so doing, may also mitigate the damaging effects of daily stress vulnerability on microvascular function.

## INTRODUCTION

The response to stressors is an integrated cascade of emotional, behavioral, and biological reactions to challenging situations aimed at protecting the body from the perceived threat

and promoting survival. On exposure to a stressful event, stress-responsive neurocircuitry initiates alterations in vigilance and emotion (e.g., fear and anxiety), activates the hypothalamus-pituitary-adrenal and sympathetic-adrenal-medullary axes, and stimulates the immune system. Although this is an evolutionarily conserved adaptive response intended to restore homeostasis, the allostatic load theory posits that the aggregate effects of frequent, repetitive, or prolonged stress system activation (or a dysregulated or excessive acute stressor response) can, through time, result in deleterious adaptations in biological function that initiate and accelerate cardiovascular disease (CVD) progression (1).

In line with this theory, a convincing body of evidence has causally established psychosocial stress as a key nontraditional risk factor precipitating the future development of CVD (2). For example, the INTERHEART study, which spanned 52 countries and included approximately 25,000 individuals, prospectively linked high amounts of psychosocial stress to an increased risk of acute myocardial infarction (3). Importantly, this association was independent of socioeconomic status, remained significant after adjusting for traditional CVD risk factors (e.g., smoking), and was largely consistent across diverse geographic regions, different age groups, and between sexes. Moreover, the link between psychosocial stress and heightened CVD-related risk was observed within multiple domains of stress, including both perceived “permanent” stress (defined by investigators as “chronic stress” resulting from conditions at work or home leading to irritability, anxiety, or difficulty sleeping) and stress related to discrete external events (defined by investigators as major life events such as marital separation or divorce, loss of job, loss of crop or business failure, major personal injury or illness, and major illness or death of a close family member or spouse) (3). Given its

Address for correspondence: Jody L. Greaney, Ph.D., 655 W. Mitchell St, Arlington, TX 76010 (E-mail: jody.greaney@uta.edu).

Accepted for publication: October 12, 2022.

Editor: Jacqueline K. Limberg, Ph.D.

0091-6331/5101/19–26

Exercise and Sport Sciences Reviews

DOI: 10.1249/JES.0000000000000310

Copyright © 2022 by the American College of Sports Medicine

ubiquity in modern society, there is, thus, an urgent need to better understand the pathophysiological mechanisms through which stress susceptibility increases CVD risk to inform more targeted therapeutic intervention strategies. Research addressing these critical gaps in knowledge is clinically important: CVD is a staggering public health challenge, occurring at an economic cost of \$378 billion, having prevalence rates of nearly 50% of adults, and remaining the leading cause of morbidity and mortality worldwide (4).

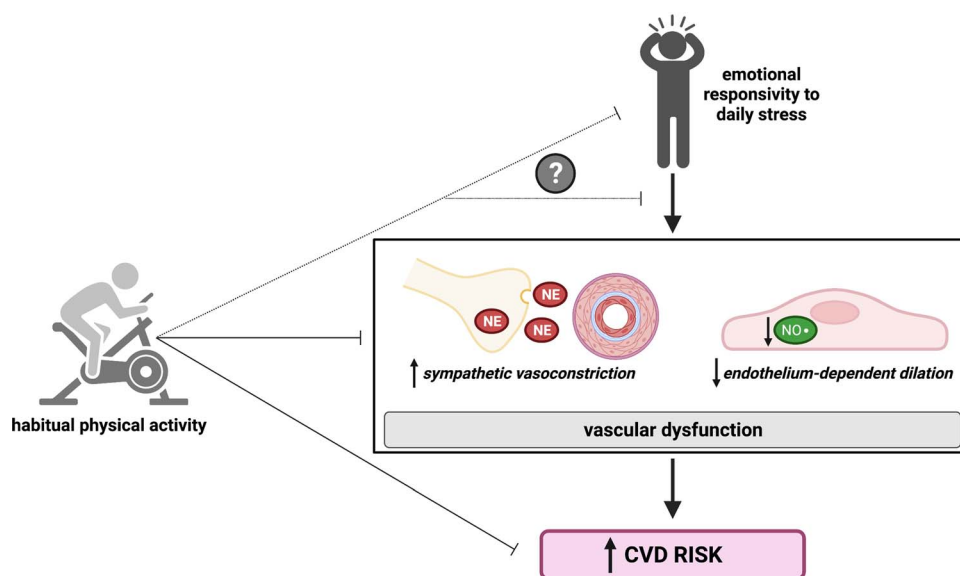
Unlike the traditional CVD risk factors (*e.g.*, age, dyslipidemia, hypertension, *etc.*), psychosocial stress is a conceptually broad framework that encompasses several different (and inter-related) elements, constructs, and domains and is thus difficult to define objectively. Perhaps not surprisingly, therefore, the measurement and quantification of stress is complex, challenging, and, in some instances, controversial (5). In this brief review, we focus exclusively on “daily stress” as a distinct and specific domain of “psychosocial stress” (defined and detailed in the next section). Our intent is to update the literature with mechanistic data from a series of studies from our laboratories that has systematically interrogated the link between daily stress and aberrant regulation of the sympathetic-immunological-cardiovascular axis of the stress response system. Specifically, we highlight our recent findings suggesting that increased emotional responsivity to daily stress is associated with a disruption in vascular homeostasis: in adults who are more responsive to daily stress, there seems to be a relative impairment in endothelium-dependent vasodilation concurrent with a sensitization of sympathetic vasoconstriction, ultimately resulting in a proconstrictor milieu (6–10). We hypothesize that these pathological alterations in the peripheral vasculature ultimately drive the development of hypertension and attendant CVD sequelae in adults who are more emotionally vulnerable to daily stress (Fig. 1). In addition, we postulate that increased habitual physical activity may mitigate these deleterious psychobiological

consequences of daily stress, thereby reducing or preventing pathophysiological CVD-related outcomes (Fig. 1). We have attempted to provide a succinct, yet comprehensive, current interpretation of this area of ongoing research. However, because of space constraints, we have cited several reviews and metaanalyses to direct the reader to additional research in this field. We gratefully acknowledge the work of our colleagues and others who have contributed to our understanding of the mechanisms through which daily stress may be linked to CVD risk and, in so doing, have advanced the field significantly. Unfortunately, we were not able to cite all relevant original research and apologize to those investigators for any oversights. As the scope of this brief review is limited, we instead only highlight those studies most foundational and relevant to the novel hypotheses presented herein.

### Daily Stress Is Ubiquitous in Everyday Life

As highlighted by several key prospective epidemiological studies, persistent long-duration chronic life stressors (*e.g.*, living in poverty, caregiving) and major life events (*e.g.*, death of a parent/child, natural disaster) predict future CVD risk (11–14). However, these types of stressors are relatively rare and not universally experienced, making the generalizability and applicability of these findings somewhat limited for determining optimal preventative interventions. In contrast, myriad everyday, commonplace, comparatively minor stressful events, or “quotidian” stressors, permeate daily life. Indeed, a growing body of literature posits that these daily stressors more strongly influence overall well-being than major, but less frequent, life events (15).

Daily stressors typically are defined as the routine challenges and concerns of day-to-day living (*e.g.*, work deadlines, daily commute) and the unexpected and episodic hassles that disrupt everyday life (*e.g.*, argument with a partner, malfunctioning computer) (16–18). In this way, daily stressors encompass both the “automatic or ritualized concerns of life” and “episodic,



**Figure 1.** Simplified schematic illustration of the novel hypothesis that pathological alterations in the peripheral vasculature — particularly excessive sympathetic vasoconstriction and blunted endothelium-dependent dilation — ultimately drive the development of hypertension and attendant cardiovascular disease (CVD) sequelae in adults who are more emotionally vulnerable to daily stress. In addition, we postulate that increased habitual physical activity may mitigate these deleterious psychobiological consequences of daily stress, thereby reducing or preventing pathophysiological CVD-related outcomes. NE, norepinephrine; NO, nitric oxide.

irregular, microevents that cannot be anticipated daily” (15). Although minor, daily stressors occur frequently — on approximately 40% of all days — and elicit separate, immediate, and direct adverse effects on emotional and physical well-being (17–19). Indeed, compared with stressor-free days, days on which daily stressors are experienced are associated with increased negative affect and symptoms of psychological distress as well as increased somatic physical health complaints (16). In general, however, both the stressor itself, as well as the emotional sequelae, tend to dissipate or disappear in a day or two (16).

There is some evidence that daily stress processes (e.g., frequency, severity, emotional responsiveness) may provide a unique explanation for stress-associated pathophysiological outcomes above and beyond either major life events in the recent past or chronic role-related life stressors (15). That is, because naturally occurring daily stressor exposures are short-lived, they can be differentiated from persistent long-duration chronic life stressors, which are open ended and typically remain constant day to day. It is important to note that the responsivity to daily stressors is not singular, and that individual and contextual factors (e.g., personality traits, socioeconomic status, history of and current exposure to chronic stress) can certainly influence both the likelihood of exposure, as well as the ensuing emotional and behavior response, to daily stress (16,18). Nevertheless, it is now apparent that daily stress has unique and independent effects from those of chronic stress that are detrimental to both psychological and physiological health and well-being (15,18,20,21). In line with this, some investigators have suggested that contextual/chronic stressors (e.g., caregiving) exert their detrimental health effects through daily stress processes (elegantly reviewed by Epel *et al.* (18)), further emphasizing the importance of examining how daily stress manifests in everyday life. A growing body of evidence also demonstrates that increased daily stress is predictive of both CVD-related and all-cause mortality, independent of personality traits and socioeconomic status (21,22). However, despite its ubiquity in everyday life, daily stress does not translate to pathological CVD-related outcomes in all individuals. Thus, it is imperative to better understand the physiological mechanisms through which daily stress increases CVD risk to advance preventative and therapeutic strategies in those who are most susceptible.

### **Emotional Responsivity to Daily Stress Predicts Chronic Disease Risk**

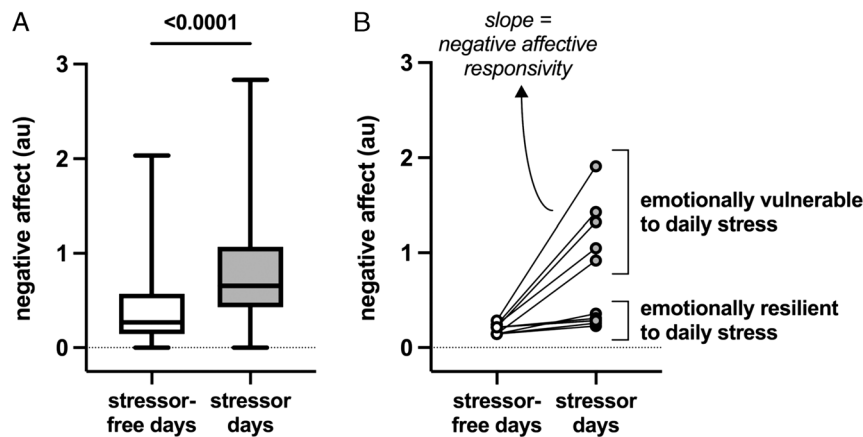
The tendency to experience negative emotions, as is characteristic of many mood and anxiety disorders (e.g., major depression), is linked to increased CVD risk (23). Building on this, it has been postulated that adults with heightened emotional vulnerability to daily stressors also may be those most susceptible to increased risk of future CVD (24). However, the evidence supporting this concept remains somewhat inconclusive, perhaps because of a reliance of many previous studies on broad, static conceptualizations of daily stress or a focus only within a specific domain (e.g., workplace) (24–28). Daily stress is a dynamic process encompassing both the exposure event (*i.e.*, the stressful event, stimulus, or circumstance) and the ensuing response to it (*i.e.*, emotional and behavioral responses). Studies using daily diary or other intensive repeated-measures methodologies to assess daily stress processes allow for the examination of the within-person coupling of daily stress events with the affective

response; in these paradigms, participants serve as their own controls (16,29). In this way, dynamic negative affective responsivity to daily stress can be conceptualized as the magnitude of the difference in a person’s negative affect on days when stressors occurred compared with stressor-free days (Fig. 2) (7). Although the negative emotional response to a singular daily stress event likely does not have strong implications for long-term health, it is indicative of how an individual typically responds to daily stress and thus reflects a trait-like pattern of emotional responsiveness that can then be used to predict between-person differences in health outcomes (25,27). A growing body of literature using this analytical approach suggests that the frequency of daily stressor occurrences by and of itself may be relatively less important for health and well-being than how an individual emotionally reacts to those events. Indeed, increased negative affective responsivity to daily stressors — but not increased stressor exposure — predicts the risk of mental health disorders, chronic medical conditions, and mortality up to a decade later (22,25,27). Importantly, this association is observed even when statistically accounting for the number of stressor exposures in the analytical models, further highlighting the importance of the magnitude of change in negative affective responsivity to daily stress within an individual for overall health and well-being.

The mechanisms linking negative affective responsivity to daily stressors to CVD risk are undoubtedly multifaceted and complex and include nonphysiological factors such as socioeconomic status, dispositional characteristics (e.g., optimism/pessimism, neuroticism, trait negative affect), psychiatric illness (e.g., depressive disorders, bipolar disorder, anxiety disorders, schizophrenia), and maladaptive health and social behaviors (e.g., insufficient sleep, substance use, social isolation), as extensively described by Epel *et al.* (18) Nonetheless, as detailed in the subsequent section, and stemming from foundational work in nonhuman primates, a series of recent studies from our laboratories has highlighted sympathetic-vascular dysfunction as a potential mechanistic underpinning of increased CVD risk in those most susceptible to the emotional consequences of daily stressor exposure. In this way, greater emotional responsivity to daily stress may further accelerate the normal age-related declines in sympathetic-vascular function, thereby predisposing an individual to increased CVD risk.

### **Psychosocial Stress and Sympathetic-Vascular Dysfunction**

Although the physiological mechanisms underlying stress-related CVD risk are multifactorial, convincing evidence implicates vascular dysfunction as a key antecedent. Indeed, seminal work in cynomolgus monkeys clearly demonstrates that chronic psychosocial stress causes endothelial dysfunction and accelerated atherosclerosis (30–32). In the experimental paradigm used in these studies, male cynomolgus monkeys were fed atherogenic diets and housed in either an unstable and stressful social setting or a normal housing environment for 2 yr. This model recapitulates two prominent dimensions of social behavior — competitiveness and aggression — thought to contribute to CVD in humans and, thus, allows for a mechanistic determination of the influence of psychosocial stress on cardiovascular outcomes. In this setting, behavioral characteristics of stress (e.g., severe aggression) were greater in the animals exposed to the stressful social conditions. In addition, the stress-susceptible animals also subsequently



**Figure 2.** Negative affect is increased on days with at least one stressor exposure compared with stressor-free days ( $n = 58$ ; box-and-whisker plots; Panel A). There is marked interindividual heterogeneity in the increase in negative affect on days with a daily stressor event compared with stressor-free days (*i.e.*, negative affective responsivity), with some individuals far more emotionally vulnerable or resilient than others ( $n = 6$  per group to aid visual clarity; Panel B). Increased negative affective responsivity to daily stressors — an index of emotional vulnerability to daily stress — predicts the risk of mental health disorders, chronic medical conditions, and mortality up to a decade later. au, arbitrary units. [Adapted from (7). Copyright © 2021 The Authors. CC-BY 4.0].

developed greater coronary artery atherosclerosis, measured by intimal lesion area in isolated vessels, than their unstressed counterparts, an effect that was independent of established CVD risk factors (*e.g.*, hyperlipidemia) (30–32). To determine the upstream mechanisms of stress-induced vascular dysfunction, the investigators next administered the nonselective beta-adrenergic receptor antagonist propranolol during the same approximately 24-month timeframe. In monkeys behaviorally susceptible to the stress-inducing conditions, the long-term inhibition of sympathetic activity abolished the development of coronary artery atherosclerosis (30), clearly demonstrating a role for the sympathetic nervous system in mediating stress-induced vascular dysfunction. The precise structural and functional consequences of sympathetic overactivity for overall vascular health, including a more thorough discussion of potential mechanistic differences across vascular beds, are beyond the scope of this brief review but have been described extensively elsewhere (33).

Building and extending this line of work, acute laboratory stressors, including mental arithmetic, lower body negative pressure, and the cold pressor test, elicit increases in sympathetic activity and subsequent decreases in large artery compliance in healthy adults (34,35), thus, likewise demonstrating a link between activation of the sympathetic arm of the stress-response system and vascular dysfunction in humans. Meta-analyses document the deleterious impact of negative affect on multiple indices of conduit artery dysfunction, including blunted endothelium-dependent dilation and increased arterial stiffness (36,37). Although it has long been speculated that impairments in vasodilatory capacity may also result from increases in negative affect secondary to stress exposure (1), to our knowledge, relatively few studies have systemically examined the interactive relation between naturally occurring stressful events (*i.e.*, experienced outside of the laboratory setting), the ensuing emotional response, and sympathetic-vascular function.

### Increased Emotional Vulnerability to Daily Stress and Sympathetic-Vascular Dysfunction

Broadly consistent with the literature noted earlier, discrete domains of daily stress (*e.g.*, workplace demands, job strain) and generalized static conceptualizations of daily stress-related

affect (*e.g.*, feelings of demand and control in daily life) also have been associated with vascular dysfunction, evidenced by increased carotid artery stiffening (26,38). These foundational studies thus link trait-measures of negative emotionality to vascular dysfunction. Extending this concept, a series of investigations from Dr. Almeida's laboratory strongly suggest that dynamic negative affective responsivity to daily stressors also influences cardiovascular health, even more so than the frequency of daily stress event occurrence (15,16,22,27,39–41).

To assess the dynamic day-to-day fluctuations in daily stress processes, Dr. Almeida and colleagues (29) have pioneered a daily diary-based approach: the Daily Inventory of Stressful Events (DISE). The DISE is an interview-based approach to measure multiple aspects of daily stress via evening telephone interviews. Participants complete the DISE interview every day for approximately eight consecutive days while free-living, with some studies expanding the assessment period up to 14 d (29,41). The DISE assesses multiple components of objective (*e.g.*, frequency, content) and subjective appraisal characteristics (*e.g.*, severity, emotions) of daily stressors. In this way, the DISE conceptually and methodologically accounts for *both* the *exposure* (*i.e.*, the stressful event, stimulus, or circumstance) and the *response* to it (*i.e.*, cognitive appraisal and emotional/behavioral responses). The interview consists of stem questions (followed by open-ended probes) asking whether any of seven types of naturally occurring psychosocial stressors occurred in the past 24 h: argument, argument avoidance, stressful event at work or school, stressful event at home, stressful event related to racial/ethnic/sexual discrimination, network stressor (*i.e.*, stressful event that happened to a close friend or relative), or any other stressful event. For each stressor, participants rate the severity, amount of control they felt, and the amount of time they spent thinking about the event as well as four negative emotions (angry, sad, nervous, shameful) during the event. The DISE also assesses daily positive and negative affect, as well as physical symptoms. This approach has been validated extensively, by us and others (for example, see (9,15,25,27,39,40,42)), and our laboratory recently has adapted the DISE to be administered using an ambulatory

Web-based application to assess daily stress processes as they unfold in everyday life, an approach that is less burdensome and more accessible than daily telephone interviews (7).

Using this approach, Almeida and colleagues have demonstrated that increased emotional vulnerability to daily stress (*i.e.*, negative affective responsivity) is linked to indirect indices of sympathetic overactivation and related downstream sequelae. For example, in a large national sample of adults ( $n = 909$ ; 35–85 yr), increased negative affective responsivity to daily stress, but not increased frequency of stressor exposure, was related to lower heart rate variability, a marker of autonomic imbalance (40). Reduced heart rate variability also has been linked to daily stress-related negative emotions in patients with coronary artery disease (43). In addition, heightened negative affective responsivity to daily stress has been strongly linked to increased concentrations of circulating inflammatory biomarkers, indicative of chronic low-grade systemic inflammation (39,44). Interestingly, as with heart rate variability, frequency of daily stressor occurrence was not related to circulating inflammatory biomarkers, providing further support for the concept that the emotional response to daily stress may be relatively more important for long-term health outcomes than exposure by and of itself.

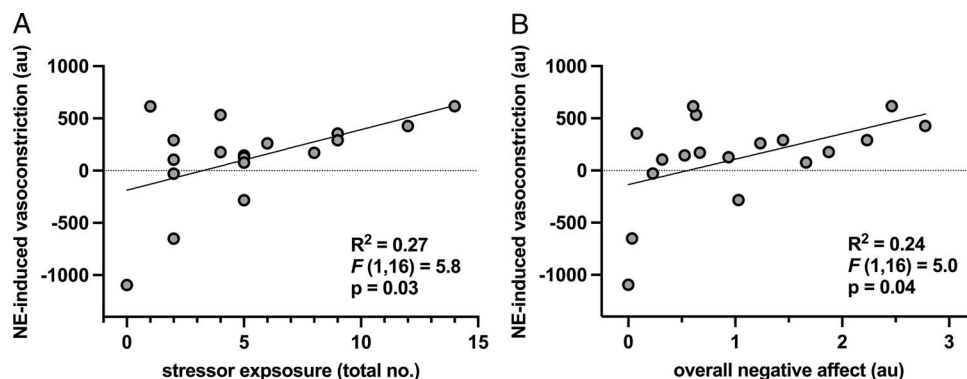
Building from this, our laboratory next investigated whether daily stress processes are linked directly to vascular dysfunction. To do so, we coupled the assessment of daily stress vulnerability while free-living with a laboratory-based *in vivo* mechanistic assessment of sympathetic vasoconstriction in the cutaneous microcirculation in college-aged young adults (9). As described earlier, young adults completed the DISE interviews, via telephone, through an 8-d time frame. On the last DISE interview day, microvascular vasoconstrictor responsiveness to exogenous norepinephrine was assessed using intradermal microdialysis coupled with laser Doppler flowmetry. During the sampling time frame, participants experienced a daily stressor on approximately 50% of days (range: 0%–88%), reporting a total of approximately five stressors during the 8-d interview period (range: 0–14 stressors) (9). Interestingly, increased frequency of daily stressor occurrence was positively related to increased norepinephrine-induced vasoconstriction (Fig. 3) (9). This finding was somewhat unexpected given the evidence described earlier suggesting that increased daily stressor exposure alone does not predict cardiovascular-related outcomes. Although the reason(s)

for this discrepancy is not readily apparent, it may be related to our use of a direct, specific, and mechanistic assessment of sympathetic vasoconstriction in immediate temporal proximity to the assessment of daily stress processes. Somewhat surprisingly, we did not detect a relation between any stressor-related negative emotions (*e.g.*, sadness, shame, anger) and norepinephrine-induced vasoconstriction (9). As this was a proof-of-concept study, the small sample size precluded the quantification of negative affective responsivity to daily stress using sophisticated two-level multilevel modeling analyses, as is typical in larger samples (39–41). However, we did note an association between overall negative affect as an index of generalized emotional health and greater sympathetic vasoconstriction (Fig. 3) (9), a finding that is broadly consistent with the hypothesis that increased emotional vulnerability to daily stress adversely influences sympathetic-vascular function.

It is important to note that our work to date has linked daily stress processes to cutaneous microvasculature function and, as such, future studies are necessary to confirm the presence (or absence) of this association in other vascular beds. For example, given its role in contributing to increased total peripheral resistance and overt hypertension, whether amplified emotional responsivity to daily stress is linked to dysfunction in the resistance arteries is of particular interest. An additional limitation of our work to date is the lack of an examination of potential sex differences in moderating the link between negative affective responsivity to daily stress and sympathetic-vascular dysfunction. As this line of research in our laboratories is still in its infancy, it likely is necessary to first validate our preliminary findings in a larger sample and determine the specific mechanistic underpinnings before establishing the influence of sex.

### Habitual Physical Activity as a Potential Buffer Against the Psychobiological Consequences of Daily Stress

Moderate amounts and intensities of habitual leisure time physical activity (*e.g.*, currently defined by the U.S. Centers for Disease Control and Prevention and American College of Sports Medicine as 150 min/wk of moderate-intensity exercise) are unequivocally associated with improved health and reduced risk of CVD morbidity and mortality (45). In addition to this well-studied cardioprotective role, habitual physical activity also seems to be a particularly effective strategy to reduce stress



**Figure 3.** The linear relation between the total number of daily stressor events over the 8-d sampling timeframe and net norepinephrine (NE)-induced vasoconstriction (expressed as area under the dose response curve; Panel A), illustrating that increased daily stressor exposure is associated with greater sympathetic vasoconstriction. Increased overall negative affect, an index of generalized emotional health, also is positively related to greater NE-induced vasoconstriction, providing broad support for the novel hypothesis that increased emotional vulnerability to daily stress adversely influences sympathetic-vascular function. [Adapted from (9). Copyright © 2020 The Authors. CC-BY-NC-ND].

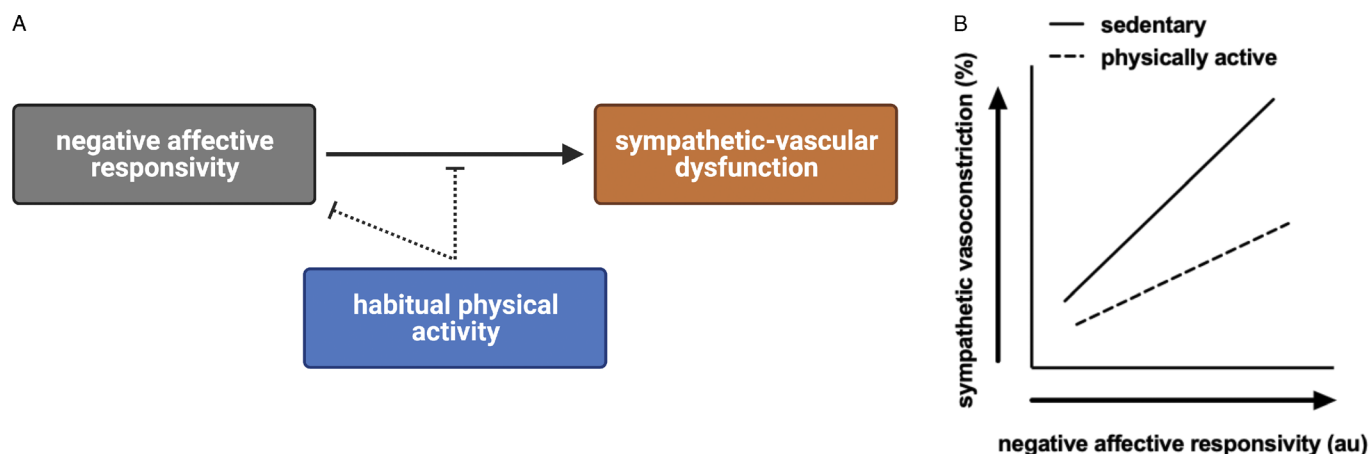
and improve emotional health. As an example of its dual beneficial role to reduce responsivity to stress, physical activity has antidepressant-like effects, such that physically fit, more active individuals seem to be both more psychologically and biologically resilient to psychosocial stressors (45). This has been demonstrated elegantly in several laboratory-based studies. In one such investigation, the Trier Social Stress Test, which consists of having participants make an interview-style presentation followed by a surprise mental arithmetic test in front of a panel of judges, was administered in a laboratory setting to both exercise-trained and untrained men (46). In both groups, the Trier Social Stress Test elicited the canonical acute stress response, including sympathetic activation and increases in anxiety. However, these effects were less pronounced in exercise-trained men, suggesting that habitual physical activity moderates stress-induced psychobiological responsiveness. An acute bout of exercise seems to offer similar benefits: 15 min of moderate-intensity cycling before viewing sad film clips (a laboratory task that reliably induces a sad mood) mitigated the increase in negative affect in adults with depression (47).

Although limited studies have specifically examined the extent to which habitual physical activity dampens negative affective responsivity to daily stress, the available literature generally confirms the aforementioned beneficial effects (42,48). Particularly strong evidence comes from a study by Almeida and colleagues that assessed daily stress using the DISE (as detailed previously) in a large national sample of approximately 2000 adults (42). Participants also reported the amount of time, the type, and the intensity of daily leisure time physical activity. Individuals who reached a degree of physical activity comparable to that recommended by the U.S. Centers for Disease Control and Prevention had blunted negative affective on both stressor and stressor-free days, as well as a significant reduction in negative affective responsivity, compared with those who did not (42). In addition, negative affective responsivity was attenuated on active compared with inactive days (42). As previously outlined, leisure time physical activity was not related to the occurrence of daily stressor events, again emphasizing the relative importance of emotional responsiveness to daily stress, and not exposure, as the primary driver of health outcomes.

As extensively reviewed elsewhere (49), there is a large body of evidence documenting the beneficial effects of habitual physical activity and exercise training on vascular function. Moreover, the existing literature clearly supports that idea that although being more physically active may not reduce the likelihood of occurrence of stressful events in everyday life, it does bolster a person's capacity to psychologically manage the stressor in a more effective way (42). However, to our knowledge, no studies to date have investigated the interactive associations between habitual physical activity, emotional responsiveness to daily stress, and sympathetic-vascular function. This is an active area of research, one which has important implications for public health and clinical care. In light of the idea introduced earlier that being more emotionally susceptible to daily stress may accelerate vascular aging, it will be imperative for future studies to consider both the influence of sex and the timing of initiation of habitual physical activity, both of which likely influence the degree to which emotional responsiveness to daily stress impairs sympathetic-vascular function across the lifespan. Regarding the former, there is some evidence that women may be more emotionally reactive to daily stressors than men (50). Compounding this, the effects of regular aerobic exercise on vascular function in postmenopausal women are not nearly as strong as those in middle-aged and older men (49). Interestingly, there has been some suggestion that supplemental estrogen treatment may be requisite to uncover the beneficial effects of aerobic exercise on vascular function in postmenopausal women (49). Whether estrogen-based hormone therapy influences negative affective responsivity to daily stress, or its link to sympathetic-vascular function, has not been determined. Secondly, there is a growing appreciation that the timing of initiating physical activity interventions also is critical. That is, adopting a more habitually active lifestyle later in life may be relatively less effective than if initiated during young or middle adulthood in dampening the detrimental effects of emotional vulnerability to daily stress on vascular health.

## CONCLUSIONS

Our work to date provides compelling support for the idea that increased emotional responsivity to daily stress is associated



**Figure 4.** Based on the available literature, we hypothesize that habitual physical activity moderates the relation between negative affective responsivity to daily stress and sympathetic-vascular dysfunction (Panel A). The predicted outcome of this model is illustrated in Panel B. In adults who engage in more regular physical activity, the slope of the relation between negative affective responsivity and sympathetic vasoconstriction will be less steep, suggesting that physical activity buffers the deleterious psychobiological consequences of daily stress.

with a disruption in vascular homeostasis, thereby highlighting a potential mechanistic underpinning of daily stress-related CVD. In addition to its direct beneficial effects on cardiovascular health, we also present preliminary evidence supporting our novel hypothesis that increased habitual physical activity has a dual role to also buffer the relation between negative affective responsivity to daily stress and sympathetic-vascular dysfunction; this is depicted conceptually in Figure 1 earlier and hypothetically in Figure 4. That is, we suggest that the slope of the relation between negative affective responsivity and sympathetic vasoconstriction is dampened in adults who engage in regular physical activity and are more fit. Following from this, we postulate that behavioral interventions to increase physical activity will elicit reductions in negative affective responsivity to daily stress concurrent with improvements in sympathetic-vascular function. Whether this can be confirmed experimentally represents an exciting line of future inquiry. Such studies will be instrumental in identifying or developing novel targeted treatment and preventative strategies to induce emotional, cognitive, and physiological resilience to daily stress, thereby mitigating current — and reducing susceptibility toward future — psychiatric, cardiovascular, and neurocognitive diseases (6–9).

## Acknowledgments

We appreciate the effort expended by the volunteer participants in those studies conducted in our laboratories, as well as the contributions of all investigators involved in the national The Midlife in the United States (MIDUS) projects. Data and documentation for all MIDUS projects are available to other researchers at the Inter-University Consortium for Political and Social Research (ICPSR). In addition to the publicly available data at ICPSR, a MIDUS-Colectica Portal ([midus.colectica.org](http://midus.colectica.org)) contains rich searchable metadata, links to helpful documentation, and the ability to download customized dataset. Figures 1 and 4 were created using BioRender.com.

Funding Disclosures: National Institutes of Health grants R00HL133414 (JLG), R21MH123928 (JLG), P01AG020166 (DMA), U19AG051426 (DMA); Health Resources and Services Administration (EFHS); The Pennsylvania State University Social Sciences Research Institute Pilot funding (DMA, JLG, and EFHS); The Pennsylvania State University Institute for Cyberscience (EFHS). Conflicts of Interest: None.

## References

- McEwen BS, Stellar E. Stress and the individual. Mechanisms leading to disease. *Arch. Intern. Med.* 1993; 153(18):2093–101.
- Kivimäki M, Steptoe A. Effects of stress on the development and progression of cardiovascular disease. *Nat. Rev. Cardiol.* 2018; 15(4):215–29.
- Rosengren A, Hawken S, Ounpuu S, et al. 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.* 2004; 364(9438):953–62.
- Tsao CW, Aday AW, Almarazoo ZI, et al. Heart Disease and Stroke Statistics-2022 update: a report from the American Heart Association. *Circulation.* 2022; 145(8):e153–639.
- Kagan J. Why stress remains an ambiguous concept: reply to McEwen & McEwen (2016) and Cohen et al. (2016). *Perspect Psychol Sci.* 2016; 11(4):464–5.
- Greaney JL, Darling AM, Mogle J, Saunders EFH. Microvascular beta-adrenergic receptor-mediated vasodilation is attenuated in adults with major depressive disorder. *Hypertension.* 2022; 79(5):1091–100.
- Greaney JL, Darling AM, Turner JR, Saunders EFH, Almeida DM, Mogle J. COVID-19-related daily stress processes in college-aged adults: examining the role of depressive symptom severity. *Front. Psychol.* 2021; 12:693396.
- Greaney JL, Koffer RE, Saunders EFH, Almeida DM, 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.* 2019; 8(4):e010825.
- Greaney JL, Surachman A, Saunders EFH, Alexander LM, Almeida DM. Greater daily psychosocial stress exposure is associated with increased norepinephrine-induced vasoconstriction in young adults. *J. Am. Heart Assoc.* 2020; 9(9):e015697.
- Greaney JL, Saunders EFH, Santhanam L, Alexander LM. Oxidative stress contributes to microvascular endothelial dysfunction in men and women with major depressive disorder. *Circ. Res.* 2019; 124(4):564–74.
- Holman EA, Silver RC, Poulin M, Andersen J, Gil-Rivas V, McIntosh DN. Terrorism, acute stress, and cardiovascular health: a 3-year national study following the September 11th attacks. *Arch. Gen. Psychiatry.* 2008; 65(1):73–80.
- Kivimäki M, Leino-Arjas P, Luukkonen R, Riihimäki H, Vahtera J, Kirjonen J. Work stress and risk of cardiovascular mortality: prospective cohort study of industrial employees. *BMJ.* 2002; 325(7369):857.
- Li J, Hansen D, Mortensen PB, Olsen J. Myocardial infarction in parents who lost a child: a nationwide prospective cohort study in Denmark. *Circulation.* 2002; 106(13):1634–9.
- Matthews KA, Gump BB. Chronic work stress and marital dissolution increase risk of posttrial mortality in men from the multiple risk factor intervention trial. *Arch. Intern. Med.* 2002; 162(3):309–15.
- Serido J, Almeida DM, Wethington E. Chronic stressors and daily hassles: unique and interactive relationships with psychological distress. *J. Health Soc. Behav.* 2004; 45(1):17–33.
- Almeida DM. Resilience and vulnerability to daily stressors assessed via diary methods. *Curr. Dir. Psychol. Sci.* 2005; 14(2):64–8.
- Bolger N, DeLongis A, Kessler RC, Schilling EA. Effects of daily stress on negative mood. *J. Pers. Soc. Psychol.* 1989; 57(5):808–18.
- Epel ES, Crosswell AD, Mayer SE, et al. More than a feeling: a unified view of stress measurement for population science. *Front. Neuroendocrinol.* 2018; 49:146–69.
- Piazza JR, Almeida DM, Dmitrieva NO, Klein LC. Frontiers in the use of biomarkers of health in research on stress and aging. *J. Gerontol. B Psychol. Sci. Soc. Sci.* 2010; 65(5):513–25.
- Nelson NA, Bergeman CS. Daily stress processes in a pandemic: the effects of worry, age, and affect. *Gerontologist.* 2021; 61(2):196–204.
- Twisk JW, Snel J, Kemper HC, van Mechelen W. Changes in daily hassles and life events and the relationship with coronary heart disease risk factors: a 2-year longitudinal study in 27–29-year-old males and females. *J. Psychosom. Res.* 1999; 46(3):229–40.
- Mroczek DK, Stawski RS, Turiano NA, et al. Emotional reactivity and mortality: longitudinal findings from the VA normative aging study. *J. Gerontol. B Psychol. Sci. Soc. Sci.* 2015; 70(3):398–406.
- Musselman DL, Evans DL, Nemeroff CB. The relationship of depression to cardiovascular disease: epidemiology, biology, and treatment. *Arch. Gen. Psychiatry.* 1998; 55(7):580–92.
- Kamarck TW, Schwartz JE, Shiffman S, Muldoon MF, Sutton-Tyrrell K, Janicki DL. Psychosocial stress and cardiovascular risk: what is the role of daily experience? *J. Pers.* 2005; 73(6):1749–74.
- Charles ST, Piazza JR, Mogle J, Sliwinski MJ, Almeida DM. The wear and tear of daily stressors on mental health. *Psychol. Sci.* 2013; 24(5):733–41.
- Kamarck TW, Muldoon MF, Shiffman S, Sutton-Tyrrell K, Gwaltney C, Janicki DL. Experiences of demand and control in daily life as correlates of subclinical carotid atherosclerosis in a healthy older sample. *Health Psychol.* 2004; 23(1):24–32.
- Piazza JR, Charles ST, Sliwinski MJ, Mogle J, Almeida DM. Affective reactivity to daily stressors and long-term risk of reporting a chronic physical health condition. *Ann. Behav. Med.* 2013; 45(1):110–20.
- Vrijkotte TG, van Doornen LJ, de Geus EJ. Effects of work stress on ambulatory blood pressure, heart rate, and heart rate variability. *Hypertension.* 2000; 35(4):880–6.
- Almeida DM, Wethington E, Kessler RC. The daily inventory of stressful events: an interview-based approach for measuring daily stressors. *Assessment.* 2002; 9(1):41–55.
- Kaplan JR, Manuck SB, Adams MR, Weingand KW, Clarkson TB. Inhibition of coronary atherosclerosis by propranolol in behaviorally predisposed monkeys fed an atherogenic diet. *Circulation.* 1987; 76(6):1364–72.
- Kaplan JR, Manuck SB, Clarkson TB, Lusso FM, Taub DM, Miller EW. Social stress and atherosclerosis in normocholesterolemic monkeys. *Science.* 1983; 220(4598):733–5.
- Williams JK, Vita JA, Manuck SB, Selwyn AP, Kaplan JR. Psychosocial factors impair vascular responses of coronary arteries. *Circulation.* 1991; 84(5):2146–53.
- Fisher JP, Young CN, Fadel PJ. Central sympathetic overactivity: maladies and mechanisms. *Auton. Neurosci.* 2009; 148(1–2):5–15.

34. Boutouyrie P, Lacolley P, Girerd X, Beck L, Safar M, Laurent S. Sympathetic activation decreases medium-sized arterial compliance in humans. *Am. J. Physiol.* 1994; 267(4 Pt 2):H1368–76.
35. Salzer DA, Medeiros PJ, Craen R, Shoemaker JK. Neurogenic-nitric oxide interactions affecting brachial artery mechanics in humans: roles of vessel distensibility vs. diameter. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* 2008; 295(4):R1181–7.
36. Cooper DC, Tomfohr LM, Milic MS, et al. Depressed mood and flow-mediated dilation: a systematic review and meta-analysis. *Psychosom. Med.* 2011; 73(5):360–9.
37. Onete V, Henry RM, Sep SJS, et al. Arterial stiffness is associated with depression in middle-aged men - the Maastricht study. *J. Psychiatry Neurosci.* 2018; 43(2):111–9.
38. Lynch J, Krause N, Kaplan GA, Salonen R, Salonen JT. Workplace demands, economic reward, and progression of carotid atherosclerosis. *Circulation.* 1997; 96(1):302–7.
39. Sin NL, Graham-Engeland JE, Ong AD, Almeida DM. Affective reactivity to daily stressors is associated with elevated inflammation. *Health Psychol.* 2015; 34(12):1154–65.
40. Sin NL, Sloan RP, McKinley PS, Almeida DM. Linking daily stress processes and laboratory-based heart rate variability in a national sample of midlife and older adults. *Psychosom. Med.* 2016; 78(5):573–82.
41. Sliwinski MJ, Almeida DM, Smyth J, Stawski RS. Intraindividual change and variability in daily stress processes: findings from two measurement-burst diary studies. *Psychol. Aging.* 2009; 24(4):828–40.
42. Puterman E, Weiss J, Beauchamp MR, Mogle J, Almeida DM. Physical activity and negative affective reactivity in daily life. *Health Psychol.* 2017; 36(12):1186–94.
43. Bacon SL, Watkins LL, Babyak M, et al. Effects of daily stress on autonomic cardiac control in patients with coronary artery disease. *Am. J. Cardiol.* 2004; 93(10):1292–4.
44. Gouin JP, Glaser R, Malarkey WB, Beversdorf D, Kiecolt-Glaser J. Chronic stress, daily stressors, and circulating inflammatory markers. *Health Psychol.* 2012; 31(2):264–8.
45. Hamer M. Psychosocial stress and cardiovascular disease risk: the role of physical activity. *Psychosom. Med.* 2012; 74(9):896–903.
46. Rimmele U, Seiler R, Marti B, Wirtz PH, Ehlert U, Heinrichs M. The level of physical activity affects adrenal and cardiovascular reactivity to psychosocial stress. *Psychoneuroendocrinology.* 2009; 34(2):190–8.
47. Mata J, Hogan CL, Joormann J, Waugh CE, Gotlib IH. Acute exercise attenuates negative affect following repeated sad mood inductions in persons who have recovered from depression. *J. Abnorm. Psychol.* 2013; 122(1):45–50.
48. Lee B, Lawson KM, Chang PJ, Neuendorf C, Dmitrieva NO, Almeida DM. Leisure-time physical activity moderates the longitudinal associations between work-family spillover and physical health. *J. Leis. Res.* 2015; 47(4):4680.
49. Seals DR, Nagy EE, Moreau KL. Aerobic exercise training and vascular function with ageing in healthy men and women. *J. Physiol.* 2019; 597(19):4901–14.
50. Birditt KS, Fingerman KL. Age and gender differences in adults' descriptions of emotional reactions to interpersonal problems. *J. Gerontol. B Psychol. Sci. Soc. Sci.* 2003; 58(4):P237–45.