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RESEARCH ARTICLE

Physiological Responses to Psychosocial Stress

Greater negative affective responsivity to daily stressors is positively related to urinary norepinephrine excretion in middle-aged adults

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Abstract

Despite mounting evidence that greater affective responsivity to naturally occurring daily stressors is associated with increased risk of cardiovascular diseases (CVDs), few studies have examined dysregulation of the sympathetic nervous system as a potential mechanism. We hypothesized that greater affective responsivity to daily stressful events would be related to increased urinary catecholamine excretion. Daily stress processes (8-day daily diary) were assessed in 715 middle-aged adults (56 ± 11 yr; 57% female) from the Midlife in the United States Study. Urinary norepinephrine and epinephrine concentrations were also measured (24 h; normalized to creatinine). Multilevel modeling was used to calculate negative and positive affective responsivity (i.e., the slope of the within-person differences in negative and positive affect on stressor days compared with stressor-free days). Analyses controlled for relevant covariates (e.g., sex, age, affect on stressor-free days, etc.). On stressor days, negative affect increased (0.1 ± 0.2 stressor-free days vs. 0.3 ± 0.4 au stressor days; $P < 0.0001$) and positive affect decreased (2.8 ± 0.7 stressor-free days vs. 2.6 ± 0.8 au stressor days; $P < 0.0001$). Greater negative affectivity responsivity to daily stressors was related to increased urinary norepinephrine ($B = 0.42$, SE = 0.14, $P = 0.003$), but not epinephrine ($P = 0.142$), excretion. Positive affective responsivity to daily stressors was not related to either urinary norepinephrine ($B = -0.33$, SE = 0.29, $P = 0.24$) or epinephrine ($P = 0.626$) excretion. Heightened negative affective responsivity to daily stressors was associated with greater urinary norepinephrine excretion, suggesting that sympathetic overactivation may contribute to the link between emotional vulnerability to daily stressors and increased CVD risk.

NEW & NOTEWORTHY Few studies have examined sympathetic dysregulation as a potential mechanism linking affective responsivity to daily stressors to future cardiovascular diseases. Using a large national sample, our findings show that amplified negative affective responsivity to daily stressors is related to increased urinary norepinephrine excretion independent of the frequency of stressor occurrence. These data suggest that chronic sympathetic overactivation may contribute to the link between emotional vulnerability to daily stressors and increased risk of future cardiovascular comorbidities.

daily stress; emotion; negative affect; norepinephrine; sympathetic nervous system

INTRODUCTION

Multiple lines of evidence have established chronic life stressors (e.g., living in poverty, caregiving) and major life events (e.g., death of a parent/child, natural disaster) as key risk factors precipitating the development of cardiovascular diseases (CVDs) (1–4). However, these types of stressors are not universally experienced and the generalizability and applicability of these findings for determining underlying mechanisms is somewhat limited. In contrast, daily stress—defined as the routine challenges and concerns of day-to-day living and the unexpected and episodic hassles that disrupt everyday life (e.g., argument with a partner, pressing work deadline)—are a distinct, but ubiquitous, source of psychosocial stress that may predict untoward CVD risk factor profiles and mortality (5–10). Although comparatively minor and mundane, daily stressors occur frequently (~40% of all days) and are reliably associated with greater negative affect and reduced positive affect on days on which they occur (6, 9, 11–13). Despite this, there is substantial heterogeneity in the magnitude of the change in affect on days on which stressor events occur compared with stressor-free days (i.e.,

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affective responsivity to daily stressors) between people, with some individuals demonstrating much larger fluctuations in negative and positive affect than others (11, 12, 14–19). This is important because how an individual affectively responds to these naturally occurring stressful experiences appears to be particularly consequential for long-term health outcomes (7, 9, 15, 20, 21).

Indeed, heightened affective responsivity to daily stressors—but not an increase in the number of stressor events themselves—predicts the risk of CVD-related mortality up to a decade later, even when accounting for chronic life stressors, personality traits, and socioeconomic status (6, 7, 9). In these studies, affective responsivity to daily stressors was operationalized as the within-person magnitude of the change in negative (or positive) affect on days on which a daily stressor occurred compared with negative (or positive) affect on stressor-free days (i.e., within-person slope) (6, 7, 9). In this way, affective responsivity to daily stressors reflects a trait-like indicator that can then be used to predict between-person differences in outcomes (6, 9). However, the psychobiological mechanisms through which greater affective responsivity to daily stressors imparts increased CVD risk remain incompletely understood.

The sympathetic-adrenal-medullary (SAM) axis plays a central role in governing the physiological response to stressor exposure (22). Its activation triggers a multifaceted and complex cascade of physiological responses, including in a surge in norepinephrine and epinephrine secretion from peripheral nerve varicosities and the adrenal medulla (22, 23). The collective result of greater concentrations of circulating catecholamines and their local effects on the vasculature, includes increases in heart rate and blood pressure, both of which prepare an organism for "fight-or-flight" in an attempt to protect against the perceived threat and promote survival (22, 24, 25). However, chronically elevated systemic concentrations of these catecholamines are indicative of excessive or prolonged SAM axis activation and directly implicated in the development of CVD (26). For instance, greater urinary norepinephrine and epinephrine excretion, considered a reliable reflection of global sympathetic activity over time (27, 28), is associated with increased risk of incident hypertension in middle-aged normotensive adults (29). Moreover, increased urinary norepinephrine excretion is evident in adults with affective disorders associated with stress system dysfunction (e.g., major depression) (30–32). Although these previous findings are broadly indicative of a relation between generalized static conceptualizations of stress-related affective dysregulation and sympathetic overactivation, our understanding of whether heightened affective responsivity, specific to daily stressors, is linked to elevated circulating catecholamine concentrations remains limited.

The goal of the current study was to examine whether affective responsivity to daily stressors is associated with urinary catecholamine excretion. To do so, we derived both negative and positive affective responsivity to daily stressors in a large national sample of middle-aged and older adults from The Midlife in the United States Study (MIDUS) (33). We hypothesized that greater negative affective responsivity (i.e., a greater within-person average increase in negative affect on stressor days compared with stressor-free days) would be positively associated with urinary norepinephrine and epinephrine excretion. We also hypothesized that greater positive affective responsivity (i.e., a greater within-person average decrease in positive affect on stressor days compared with stressor-free days) would be negatively related to urinary norepinephrine and epinephrine excretion.

METHODS

Participants

Data for the current analyses are from the second wave of The Midlife in the United States Study (MIDUS II; 2004–2006), including the National Study of Daily Experiences II (NSDE) and Biomarker Project (33). All study procedures were reviewed and approved by the Educational and Social/Behavioral Science and Health Sciences Institutional Review Boards at the University of Wisconsin-Madison and The Pennsylvania State University. Documentation and de-identified data for all MIDUS projects are publicly available at the Inter-university Consortium for Political and Social Research (ICPSR; https://www.icpsr.umich.edu/icpsrweb). Research materials and analytic code for the present investigation are available upon reasonable request.

A total of 1,011 participants completed both the NSDE II (an intensive daily diary study across ~8 consecutive days) and the Biomarker Project (a clinical laboratory study to examine psychobiological health outcomes in controlled hospital setting). From this sample, 921 participants reported at least one stressor day and at least one stressor-free day over the sampling timeframe, allowing for the calculation of affective responsivity slopes (described in *Assessment of Daily Stress Processes and Daily Affect*). Additional participants were excluded for missing urinary catecholamine data ($n = 15$). Taking a conservative approach, participants with missing or uncertain data for relevant predictors ($n = 7$; stressor occurrence, daily negative affect, daily positive affect) or covariates (sociodemographic parameters and physical health factors, $n = 112$; medication usage, $n = 72$) were also excluded. This resulted in a final sample size of 715 for analyses.

Assessment of Daily Stress Processes and Daily Affect

Daily stress processes were assessed using the Daily Inventory of Stressful Events (DISE) (34). The DISE interview was administered via telephone each evening for 8 consecutive days to assess objective (e.g., frequency and content) and subjective appraisal characteristics (e.g., severity, negative emotions) of daily stressors (Fig. 1*A*). Participants reported whether any of six types of stressors occurred in the past 24 h: argument, argument avoidance, stressful event at work or school, stressful event at home, network stress (i.e., stressful event that happened to a close friend or relative), or any other stressor. Because the DISE captures both specific events and the ensuing responses in the immediate 24 h preceding each daily assessment, it is uniquely focused on the types of hassles that result from everyday life and not chronic stress or major life events (34). Obtaining daily stressor information over this short time frame helps alleviate concerns with ecological validity and retrospective memory bias (35). Consistent with the approach in our previous work (6, 9, 12, 16, 17, 19, 36), days on which an individual reported at least one stressor were coded as "stressor days" and days

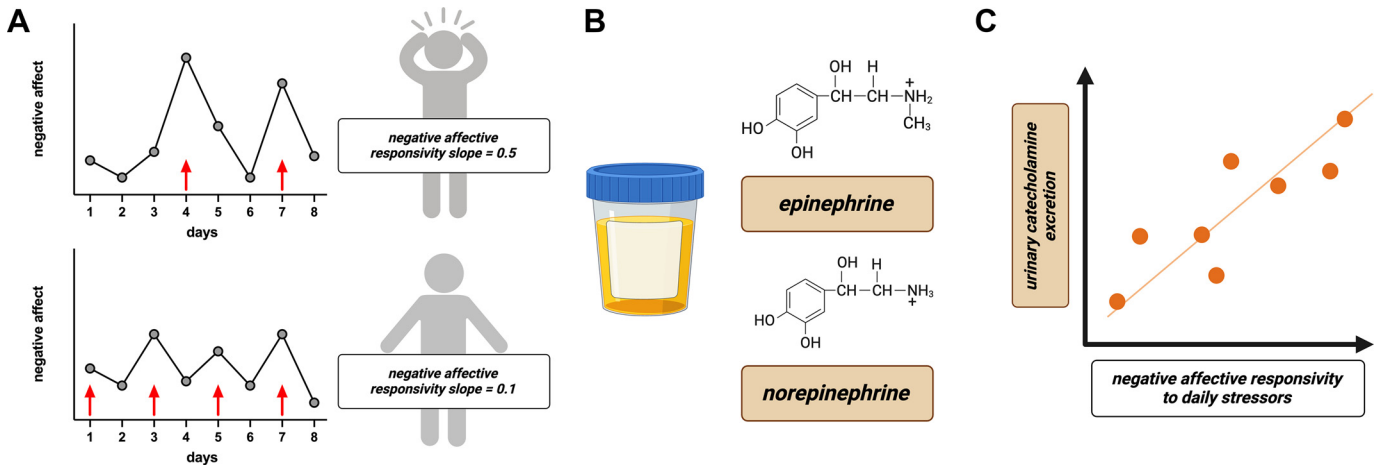

Figure 1. *A*: cartoon representation of the assessment of daily stress processes and daily negative (and positive) affect in 2 hypothetical participants. Daily stress processes were assessed using the Daily Inventory of Stressful Events interview, which was administered by telephone each evening for 8 consecutive days. Participants reported whether any of 6 types of stressors occurred in the previous 24 h. Days on which an individual reported at least one stressor were coded as "stressor days" (indicated by red arrows) and days on which an individual did not report any stressors were coded as "stressor-free days." Daily negative (and positive) affect was calculated each day. Negative (and positive) affective responsivity to daily stressors was operationalized as the magnitude of the within-person change in affect on days when stressors occurred compared with one's typical affect on stressor-free days (i.e., slope). The multilevel model used to derive affective responsivity to daily stressors calculated affect on stressor-free days (intercept) and the individual-specific change in affect on daily stressor days (random slope). Using this analytical approach, a greater negative (or positive) affective responsivity slope is indicative of an individual having relatively greater increases in negative affect (or decreases in positive affect) on stressor days compared with stressor-free days. *B*: participants also separately completed a one-time laboratory-based measurement of urinary catecholamine excretion. *C*: for the primary analyses, general linear models were estimated to determine whether model-estimated negative (and positive) affective responsivity to daily stressors was associated with urinary catecholamine excretion. These linear regression models accounted for both the total number of stressor days reported over the sampling timeframe and affect on stressor-free days. Figure created with a licensed version of Biorender.com.

on which an individual did not report any stressors were coded as "stressor-free days" (Fig. 1*A*).

Daily negative and positive affect were also assessed on each interview day (37). Participants indicated how often they experienced any of 14 negative emotions (restless or fidgety, nervous, worthless, so sad nothing could cheer you up, everything was an effort, hopeless, lonely, afraid, jittery, irritable, ashamed, upset, angry, and frustrated) and 13 positive emotions (in good spirits, cheerful, extremely happy, calm and peaceful, satisfied, full of life, close to others, like you belong, enthusiastic, attentive, proud, active, and confident) using a 5-point Likert scale (0 = none of the time, 1 = a little of the time, 2 = some of the time, 3 = most of the time, 4 = all of the time). Daily negative and positive affect were calculated separately by averaging the respective items each day (Fig. 1*A*); scores were subsequently used to create an average daily affect score over the entire sampling timeframe. In addition, daily negative and positive affect on stressor days and on stressor-free days were then separately derived in the same manner. Because negative and positive affect were assessed daily, we computed the reliability of these measures following standard guidelines for repeated measures (i.e., the proportion of variance due to individual differences relative to the total variance in the model after correcting the error variance for the repeated occasions) (38). Reliability for both negative and positive affect was high (negative affect reliability = 0.86; positive affect reliability = 0.96).

Affective responsivity to daily stressors was operationalized as the within-person difference in affect on days when stressors occurred compared with affect on stressor-free days (i.e., within-person slope; Fig. 1*A*) (6, 9, 12, 16, 17, 19). Following analytical procedures established in other studies using the MIDUS cohort (12, 19), unique affective responsivity slopes were calculated for each individual using a two-level multilevel model in which daily stressor exposure (0 = days during which no daily stressors occurred; 1 = days during which at least one daily stressor occurred) was entered as a predictor of daily affect on *day d* for person *i*, while accounting for the total number of daily stressor days:

Level 1 (day-level):

$$\text{Negative/Positive Affect}_{di} = a_{0i} + a_{1i}(\text{Stressor Day}_{di}) + e_{di}$$

Level 2 (person-level):

$$a_{0i} = \beta_{00} + u_{0i}$$

$$a_{1i} = \beta_{10} + u_{1i}$$

At *level 1*, a_{0i} is the intercept (negative or positive affect on stressor-free days), a_{1i} is the affective responsivity slope (person *i*'s difference in negative or positive affect on stressor days compared with stressor-free days), and e_{di} is the error (person *i*'s day-to-day variability in negative or positive affect). Daily stressor exposure (Stressor Day_{di}) was modeled as a random effect. At *level 2*, β_{00} is the average negative or positive affect, β_{10} is the negative or positive affective responsivity slope for the sample, and u_{0i} and u_{1i} are the variances (person *i*'s deviations from the sample average of negative or positive affect and negative or positive affective responsivity; i.e., the random effects). Using this analytical approach, a greater negative affective responsivity slope (i.e., a more positive value) is indicative of an individual having relatively greater increases in negative affect on stressor days compared with stressor-free days, whereas a greater positive affective responsivity slope

(i.e., a more negative value) is indicative of an individual having relatively greater decreases in positive affect on stressor days compared with stressor-free days. For example, a person having a negative affective responsivity slope of 0.17 (the sample average) had an increase in negative affect of 0.17 on stressor days relative to stressor-free days (12). This calculation requires that a person report both stressor and stressor-free days over the sampling timeframe. Affective responsivity slopes could not be computed for 90 participants (~9% of the sample: 71 participants reported not experiencing any daily stressors and 19 participants reported a daily stressor event every day). These unique individual affective responsivity slopes (i.e., a_{1i} in the aforementioned equation) were subsequently entered as predictors in the linear regression models for the primary analyses described later.

Assessment of Urinary Catecholamine Excretion

Participants completed a one-time laboratory-based measurement of urinary catecholamine excretion (separate from the 8-day assessment of daily stress processes and daily affect; Fig. 1*B*) at one of three General Clinical Research Centers (University of California Los Angeles, Los Angeles, CA; Georgetown University, Washington, D.C.; University of Wisconsin, Madison, WI), using an identical protocol standardized for all MIDUS Biomarker study sites (33). A 12-h overnight (7:00 PM to 7:00 AM) urine sample was collected and stored in a container filled with 25 mL of 50% acetic acid. These acidified and untreated urine samples (13 mL aliquots) were stored in a −60°C to −80°C freezer and shipped to the MIDUS Biocore monthly. Urinary norepinephrine and epinephrine concentration were measured using high-performance liquid chromatography (HPLC), as previously described (39). To reduce variability, all urinary catecholamine analyses were adjusted for urinary creatinine concentration (29, 40); urinary creatinine concentrations were measured at the Mayo Clinic Medical Laboratory using a commercially available enzymatic colorimetric assay kit (29). Mean inter- and intra-assay coefficients for norepinephrine excretion were 6.7%–6.9% and 8% and for epinephrine excretion were 7.8%–7.9% and 8%; the inter-assay coefficient for creatinine concentration was 0.85% (the intra-assay coefficient for creatine is not available). Urinary norepinephrine and epinephrine concentrations were log-transformed for normality. However, for clarity of visual interpretation, we present results using nontransformed data.

Data and Statistical Analyses

Data were cleaned and managed in R and analyzed in SAS 9.4. (SAS PROC MIXED). Descriptive statistics were calculated for all outcome variables and, next, their correlations to negative and positive affective responsivity to daily stressors were examined to determine the direction and the strength of linear associations. For the primary analyses, general linear models were estimated to determine whether negative and positive affective responsivity to daily stressors were associated with urinary catecholamine excretion (Fig. 1*C*). All linear regression models were adjusted for negative and positive affect on stressor-free days and the total number of daily stressor days reported over the sampling timeframe (6, 9, 12, 19).

Linear regression analyses also controlled for covariates that were measured in all participants and may influence SAM axis function, including *1*) sociodemographic factors: age (continuous; mean-centered), self-reported biological sex (0 = female, 1 = male), race (0 = non-white, 1 = white), marital status (0 = not married, 1 = married), annual household income (continuous; mean-centered), highest level of education achieved (0 = no school/some grade school, 1 = eighth grade/junior high school, 2 = some high school, 3 = GED, 4 = graduated from high school, 5 = 1–2 yr of college, 6 = 3 or more years of college, 7 = graduated from 2-yr college/vocational school, 8 = graduated from a 4- or 5-yr college/bachelor's degree, 9 = graduate school, master's degree, Ph.D./ED.D./other professional degree), and employment status [0 = unemployed (including retired or not working by choice), 1 = employed]; *2*) physical health factors: number of chronic health conditions relevant to the central nervous system or cardiovascular health (e.g., heart disease, high blood pressure, circulatory diseases, blood clots, heart murmur, transient ischemic attack or stroke; continuous; mean-centered), body mass index (continuous; mean-centered), and the use of medications that can influence the central nervous system (e.g., analgesics, anticonvulsants, antivertigo antiemetic agents, antiparkinsonian agents, central nervous system stimulants, miscellaneous central nervous system agents, or cholinesterase inhibitors; 0 = no, 1 = yes); *3*) psychological health: depression symptoms assessed via the Center for Epidemiologic Studies Depression scale [continuous; mean-centered; (41)] and neuroticism assessed via the Midlife Development Inventory Personality scale [continuous; mean-centered; (42)]; and *4*) health behaviors: whether participants were ever regular smokers (0 = no, 1 = yes), whether participants currently exercise 20 min or more at least three times per week (0 = no, 1 = yes), and overall sleep quality assessed via the Pittsburgh Sleep Quality Index [continuous; mean-centered (43)].

All covariates remained consistent across all analyses, and continuous variables were centered at the sample mean. Predictors and covariates were added simultaneously in all models. Significance was set at $\alpha < 0.05$ and data are presented as means ± standard deviation.

RESULTS

Participants were 56 ± 11 yr and 57% of the sample were female (Table 1). Additional descriptive information about the sample is presented in Table 1, including the correlations between covariates and negative and positive affective responsivity slopes. Participants reported experiencing a daily stressor on 41 ± 21% of days, with an average of 3 ± 2 total stressor days across the sampling timeframe. On stressor days, negative affect was greater (0.1 ± 0.2 stressor-free days vs. 0.3 ± 0.4 au stressor days; $P < 0.0001$; Table 1) and positive affect was reduced (2.8 ± 0.7 stressor-free days vs. 2.6 ± 0.8 au stressor days; $P < 0.0001$; Table 1). This corresponded to an average negative affective responsivity slope of 0.17 ± 0.1 and a positive affective responsivity slope of −0.14 ± 0.05 for the study sample (Table 1). That is, on average, participants reported a statistically significant increase in negative affect of 0.17 units and a statistically significant decrease in positive affect of 0.14 units on stressor days

Table 1. *Descriptive statistics and their correlation with affective responsivity to daily stressors*

Variable (n = 715)	Mean (SD)	Correlation Coefficients	
		Negative Affective Responsivity	Positive Affective Responsivity
Age, yr	55.9 (11.4)	−0.174**	0.063
Female	56.6%	−0.037	0.044
Married	73.4%	−0.061	−0.016
Employed	53.3%	0.027	0.013
White	93.5%	−0.017	−0.039
More than high school education	76.9%	−0.030	−0.038
Total household income, $	77,978 (59,391)	−0.034	0.008
Ever smoked regularly	11.2%	0.127**	−0.031
Habitual exercisers	79.0%	−0.078*	−0.025
Sleep quality, au	0.97 (0.67)	0.146**	−0.094*
Current use of CNS-acting medications	67.1%	−0.020	0.012
Body mass index, kg/m^2	29.3 (6.0)	0.026	0.021
CES-D, au	8.1 (8.0)	0.328**	−0.059
Neuroticism, au	2.0 (0.6)	0.287**	−0.112**
Chronic health conditions (total number)	0.81 (1.0)	−0.045	0.072
Daily stressor days (total)	3.3 (1.7)	0.129**	−0.019
Total daily stressors (sum)	4.7 (4.1)	0.10**	0.011
Negative affect (stressor days)	0.3 (0.3)		
Negative affect (stressor-free days)	0.1 (0.2)		
Positive affect (stressor days)	2.6 (0.7)		
Positive affect (stressor-free days)	2.8 (0.7)		
Urinary norepinephrine, mg/g creatinine	27.6 (13.2)	0.010**	−0.069
Urinary epinephrine, mg/g creatinine	2.0 (1.2)	0.007	−0.010
Negative affective responsivity	0.17 (0.12)		−0.334**
Positive affective responsivity	−0.14 (0.05)	−0.334**	

See text for a complete description of how covariates were coded for statistical analyses. au, arbitrary units; CES-D, Center for Epidemiologic Studies Depression scale; CNS, central nervous system; SD, standard deviation. *$P < 0.05$; **$P < 0.01$.

compared with stressor-free days (Table 1). The total number of daily stressor exposure days was correlated with negative ($r = 0.129$, $P < 0.01$), but not positive ($r = -0.019$, $P = 0.620$), affective responsivity to daily stressors (Table 1). Urinary norepinephrine and epinephrine concentrations are also reported in Table 1.

Results from the linear regression models examining the relations between affective responsivity to daily stressors and urinary catecholamine excretion appear in Table 2. Consistent with our hypothesis, greater negative affective responsivity to daily stressors (i.e., greater negative affect on stressor days compared with stressor-free days) was associated with greater urinary norepinephrine excretion (B = 0.42, SE = 0.14, 95% CI [0.14, 0.70], P = 0.003; Table 2 and Fig. 2*A*) but not urinary epinephrine excretion ($B = 0.18$, SE = 0.12, 95% CI [−0.06, 0.43], $P = 0.14$; Table 2). For example, a 0.17-unit increase in negative affect on stressor days compared with stressor-free days (the sample mean) was associated with a 1.18 mg/$g_{creatinine}$ greater urinary norepinephrine excretion (note: catecholamine values were log-transformed for normality prior to analyses and were exponentiated for ease of interpretation). There were no associations between positive affective responsivity to daily stressors and either urinary norepinephrine ($B = -0.33$, SE = 0.29, 95% CI [−0.90, 0.23], $P = 0.24$; Table 2 and Fig. 2*B*) or epinephrine excretion ($B = -0.12$, SE = 0.25, 95% CI [−0.61, 0.37], $P = 0.63$; Table 2).

DISCUSSION

Our findings suggest that greater negative, but not positive, affective responsivity to daily stressors predicts greater urinary norepinephrine excretion, even when controlling for the number of reported stressor occurrences and relevant covariates known to influence sympathetic nervous system function. Neither negative nor positive affective responsivity to daily stressors were associated with urinary epinephrine excretion. Collectively, this suggests that a larger magnitude in the change in daily stressor-related negative affect is associated with chronic sympathetic overactivation, regardless of the frequency of days on which a daily stressor occurs. These data are the first to directly link negative affective responsivity to naturally occurring stressors arising out of routine day-to-day living to alterations in the sympathetic arm of the stress response system, thereby providing potential mechanistic insight into daily stress-related CVD risk (36).

Tonic rhythmic discharge of sympathetic nerves is critical for the regulation of vasomotor tone and is thus essential for appropriate blood pressure regulation (26). In addition, acute exposure to psychological and physiological stressors activates the SAM axis, and the resultant secretion of the sympathetic neurotransmitters norepinephrine and epinephrine has direct cardiostimulatory effects, mediated via peripheral adrenergic receptors (primarily α_1 and β_1), to prepare the organism for "fight or flight" (22, 24, 25). Thus, circulating catecholamine concentrations are generally thought to accurately reflect global sympathetic activity. Chronically elevated sympathetic outflow at rest and an excessive (or prolonged) sympathetic response to acute stress exposure are thought to result in deleterious adaptations that may initiate and accelerate CVD progression (22, 26). Urinary catecholamine excretion provides a particularly reliable integrated assessment of sympathetic function over time and overcomes many of the limitations of measures of plasma concentrations of norepinephrine and epinephrine (27, 28). Therefore, greater urinary catecholamine excretion is considered a biological indicator of persistent overstimulation of

Table 2. *Linear associations between urinary catecholamine excretion and affective responsivity to daily stressors (n = 715)*

	Urinary Norepinephrine Excretion				Urinary Epinephrine Excretion			
	Negative Affective Responsivity		Positive Affective Responsivity		Negative Affective Responsivity		Positive Affective Responsivity	
Variable	*B*	SE	*B*	SE	*B*	SE	*B*	SE
Intercept	3.40**	0.08	3.25**	0.11	1.05**	0.07	0.87**	0.10
Predictor								
Affective responsivity	0.42**	0.14	−0.33	0.29	0.18	0.12	−0.12	0.25
Covariates								
Affect on stressor-free days	−0.16	0.09	0.05*	0.03	−0.12	0.08	0.07**	0.02
Age	0.01**	0.00	0.01**	0.00	0.00*	0.00	0.00*	0.00
Sex	−0.28**	0.03	−0.27**	0.03	−0.05*	0.03	−0.05	0.03
Marital status	−0.05	0.04	−0.05	0.04	0.01	0.03	0.01	0.03
Employment status	−0.02	0.03	−0.02	0.03	0.01	0.03	0.02	0.03
Race	−0.04	0.06	−0.04	0.06	−0.02	0.06	−0.02	0.05
Education status	−0.00	0.01	−0.00	0.01	0.00	0.01	0.00	0.01
Total household income	0.00	0.00	0.00	0.00	−0.00	0.00	−0.00	0.00
Ever smoked regularly	0.17**	0.05	0.18**	0.05	0.01	0.04	0.02	0.04
Habitual exercise	−0.04	0.04	−0.03	0.04	0.02	0.03	0.03	0.03
Sleep quality	0.01	0.02	0.00	0.02	−0.02	0.02	−0.02	0.02
Current use of CNS-acting medications	−0.01	0.03	−0.01	0.03	−0.03	0.03	−0.03	0.03
Body mass index	0.00	0.00	0.00	0.00	−0.01**	0.00	−0.01**	0.00
CES-D	−0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Neuroticism	−0.02	0.03	−0.01	0.03	0.02	0.02	0.03	0.02
Chronic health conditions	0.03*	0.02	0.03*	0.02	0.02	0.01	0.02	0.01
Daily stressors	−0.00	0.01	0.00	0.01	−0.00	0.01	0.00	0.01

See text for a complete description of how covariates were coded for statistical analyses. *B*, unstandardized regression coefficient; CES-D, Center for Epidemiologic Studies Depression scale; CNS, central nervous system; SE, standard error. *$P < 0.05$; **$P < 0.01$.

the sympathetic nervous system. Moreover, higher urinary catecholamine excretion predicts functional decline and mortality in healthy community-dwelling older adults (44) and incident hypertension (29, 45).

Despite a large body of work linking daily stress processes—especially affective responsivity—to an increased risk of myriad deleterious CVD-related health outcomes (5–10, 12, 19, 46), the underlying mechanisms remain incompletely understood and surprisingly few investigations have specifically examined a potential association between affective responsivity to daily stressors and sympathetic overactivity. Previous work has found that a more pronounced negative affective response to daily stressors is associated with blunted heart rate variability in middle-aged and older adults (12, 47, 48). However, a link between stress-related negative affect and heart rate variability is not a universal finding (49), and, although reduced heart rate variability is a marker of cardiac autonomic imbalance, its usefulness for understanding and quantifying the integration between sympathetic and parasympathetic function in mediating these alterations is limited (50).

The tendency to experience negative emotions, as is characteristic of many affective disorders associated with stress system dysfunction (e.g., major depression, posttraumatic stress disorder), is associated with generalized sympathetic overactivation (30, 31, 51–54). Our results now show that this association also extends more specifically to exaggerated negative affective responsivity to daily stressors. Furthermore, in alignment with renewed calls for rigor and reproducibility in biomedical research, these findings demonstrate consistency with the prior studies that have shown a link between affective responsiveness to multiple different types and sources of psychosocial stress and disruptions in the regulation of tonic sympathetic outflow. Given our previous work indicating that both a greater frequency of days with a daily stressor event and a greater total number of stressor events were each related to increased norepinephrine-induced vasoconstriction (36), we are now exploring the degree to which negative affective responsivity to daily stressors may also translate to excessive sympathetic vasoconstriction.

One distinctive advantage of the daily diary approach use herein is that we conceptually and methodologically accounted for both the stressor exposure (i.e., the stressful event, stimulus, or circumstance) and the response to it (i.e., cognitive appraisal and affective/behavioral adaptations). This intensive repeated-measures design allowed for a precise examination of the within-person coupling of daily stressor events with the ensuing affective response. In these paradigms, participants serve as their own controls, allowing for the calculation of within-person affective responsivity slopes that can then be used to predict between-person differences in health outcomes (11, 34). Consistent with the analytical approach developed by Almeida and colleagues (7, 9, 11, 12, 19, 46), we operationalized affective responsivity to daily stress as the magnitude of the difference in a person's negative (or positive) affect on days when stressors occurred compared with stressor-free days. The current findings indicate that greater negative, but not positive, affective responsivity to daily stressors (i.e., more of an increase in negative affect but not more of a decrease in positive affect on stressful days) is linearly related to greater urinary norepinephrine excretion, but not urinary epinephrine excretion. The reason for this discrepancy is not readily apparent but may potentially be related to the frequent dissociation between the magnitude of the systemic norepinephrine and epinephrine response to different

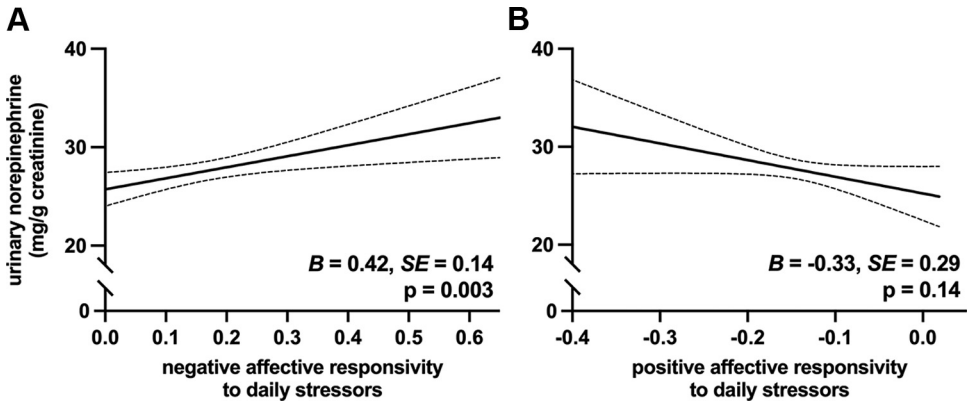

Figure 2. The linear relation between negative (*A*) and positive (*B*) affective responsivity to daily stressors and urinary norepinephrine excretion. Negative (and positive) affective responsivity to daily stressors was operationalized as the magnitude of the within-person change in affect on days when stressors occurred compared with one's typical affect on stressor-free days (i.e., slope; multilevel modeling). A greater negative affective responsivity slope (i.e., a more positive value) is indicative of an individual having a relatively large increase in negative affect on days with a stressor event; a greater positive affectivity slope (i.e., a more negative value) is indicative of an individual having a relatively large decrease in positive affect on days with a stressor event. Greater negative, but not positive, affective responsivity predicted increased urinary norepinephrine excretion in a large national sample of middle-aged and older adults ($n = 715$). The regression line and 95% confidence intervals are depicted. Absolute values of catecholamine excretion (normalized to creatinine) are presented for visual clarity; however, model outputs are reported for the log-transformed values.

stress stimuli (23, 55, 56). Plasma norepinephrine is primarily derived from sympathetic nerve terminals, whereas plasma epinephrine is primarily derived from the adrenal medulla, so we speculate that daily stressors may perhaps elicit differential stimulation of the sympathetic nervous system proper relative to the adrenal medulla (23).

Somewhat unexpectedly, positive affective responsivity to daily stressors was not predictive of blunted urinary catecholamine excretion. Although negative and positive affect are distinct constructs that only weakly correlate with each other (57), greater daily positive affect is associated with a lower risk of future disease and mortality, independent from the deleterious effects of daily negative affect (58, 59). Furthermore, a relative failure to maintain positive affect in the face of daily stressors is associated with chronic systemic inflammation (14, 19). It is possible that greater positive affective responsivity to daily stressors (i.e., a relatively smaller change in positive affect on daily stressor days compared with stressor-free days) may be more strongly related to other nonsympathetic-mediated aspects of the stress response system (e.g., immune system activation, hypothalamic-pituitary axis function). This merits prospective investigation.

We also observed a role for sex in predicting urinary catecholamine excretion, such that both urinary norepinephrine and epinephrine excretion were greater in females compared with males. Whether there are sex differences in urinary norepinephrine and epinephrine remains equivocal (60–63), making interpretation of our findings somewhat difficult. Although there is some evidence for sex differences in affective responsivity to daily stressors (16, 64), it is important to note that because our analyses only tested for a main effect of affective responsivity on urinary catecholamine excretion—and not an interaction between sex and affective responsivity—our data preclude a more definitive understanding of whether sex moderates the relation between negative affective responsivity to daily stressors and urinary norepinephrine excretion. Although outside the scope of the present study, this merits future investigation.

There are several study limitations that warrant consideration. First, as indicated earlier, we did not assess whether any covariates are moderators of the relation between affective responsivity and urinary catecholamine excretion. In addition, the current analyses are not powered to evaluate interaction effects between all possible covariates and the variables of interest. Thus, given the interactive nature of several covariates (e.g., obesity and nicotine use), caution is warranted when interpreting the effect of any covariate in isolation in the analyses presented herein. Note that our intent was to instead take the step of first establishing associations between the primary outcome variables, thereby setting the stage for prospective investigations to determine how personal characteristics might impact these linkages. In line with this, an important line of future inquiry includes a more nuanced understanding of whether and how "baseline" daily affect in general influences urinary catecholamine excretion. Second, we cannot determine the causality or direction of these associations due to the observational nature of the study design. Finally, because affect was assessed at the end of each day, it is not possible to determine the degree to which affective responsivity to daily stressors reflects the concurrent emotional responses to stressful events as they happen in real-time or if it instead represents either prolonged emotional activation or slower emotional recovery (65). Regardless, these constructs may compound one another, exacerbating affective dysregulation. To address this and to disentangle same-day (concurrent) and carryover (lagged) effects, temporally sensitive future studies are necessary. Although such ecological momentary assessment protocols may provide greater specificity of affective responsivity to daily stress events, the daily diary approach used herein captures the typical daily experience over an extended sampling timeframe and is thus reflects a trait-like pattern of emotional responsiveness that can then be used to predict between-person differences in health outcomes (6, 9). Studies designed to examine the interactive effects of daily stressor exposure, diversity of stressor subtypes, affective responsivity, and residue (i.e., persistent emotional reactivity) are warranted.

Conclusions and Perspectives

Using an ecologically rigorous assessment of affective responsivity to daily stressors in a large national sample of middle-aged adults, we demonstrated a link between greater negative, but not positive, affective responsivity to daily stressors and greater urinary norepinephrine excretion. These data suggest that a greater negative affective response to days on which a daily stressor occur is associated with chronic sympathetic overactivation, which may be a potential contributor to the link between daily stress and CVD morbidly and mortality. Interestingly, therapeutic intervention strategies to alleviate or buffer the detrimental emotional consequences of stress exposure may secondarily reduce sympathetic outflow (66–68). In this context, the present findings provide an experimental basis for designing clinical trials to determine whether improving resiliency to the common, yet pervasive, stressors in everyday life also reduces sympathetic activity and improves the CVD risk profile in middle-aged adults.

DATA AVAILABILITY

Data for all MIDUS projects are publically available. Analytic code for the present investigation is available upon reasonable request.

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

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AUTHOR CONTRIBUTIONS

D.M.A. and J.L.G. conceived and designed research; E.M.G., J.H.H., J.M., and J.L.G. analyzed data; E.M.G., J.H.H., J.M., D.M.A., and J.L.G. interpreted results of experiments; J.H.H. and J.L.G. drafted manuscript; J.L.G. prepared figures; E.M.G., J.H.H., J.M., D.M.A., and J.L.G. edited and revised manuscript; E.M.G., J.H.H., J.M., D.M.A., and J.L.G. approved final version of manuscript.

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