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Psychobiological Reactivity to Acute Psychological Stress as a Predictor of Cardiovascular Disease and Mortality: The Multi-Ethnic Study of Atherosclerosis

Running Title: Stress Reactivity and Clinical Outcomes

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ABSTRACT

INTRODUCTION

Dysregulated psychobiological reactivity to acute psychological stress is associated with subclinical cardiovascular disease (CVD) risk, but its link to clinical CVD and mortality remains unclear—especially when considering both exaggerated and blunted responses, non-cardiovascular biomarkers, and potential racial/ethnic differences. This study aimed to test (1) relationships between multi-system stress reactivity and CVD/mortality, and (2) effect modification by race/ethnicity.

METHODS

Participants were CVD-free adults (N=957, age=69±9 years, 56% female, 27% non-Hispanic White, 32% non-Hispanic Black, 41% Hispanic) enrolled in the Multi-Ethnic Study of Atherosclerosis. The following responses to a standardized psychological stress protocol were recorded: blood pressure (BP), heart rate, heart rate variability (HRV), salivary alpha-amylase (sAA), and cortisol. Participants were followed for a median of 8 years. Covariate-adjusted Cox proportional hazard models investigated associations of stress reactivity (low/blunted: ≤25th percentile; intermediate/moderate [reference]: 26-74th; high/exaggerated: ≥75th) with incident CVD (N=111) and all-cause mortality (N=114). Race/ethnicity was tested as an effect modifier.

RESULTS

Stress reactivity was not associated with CVD incidence. Blunted diastolic BP reactivity was associated with premature all-cause mortality (HR=1.92, 95% CI: 1.03—3.56). Exaggerated (HR=0.58, 95% CI: 0.35—0.98) and blunted (HR=0.52, 95% CI: 0.30—0.89) sAA reactivity were associated with reduced mortality risk. Race/ethnicity was not an effect modifier (all *p* for interaction > 0.05).

DISCUSSION

Targeted interventions to improve blunted DBP reactivity may help mitigate premature mortality. Further research should explore why dysregulated sAA reactivity was associated with lower mortality risk.

KEY WORDS

Health disparities, acute stress, physiological responses, chronic disease prevention, stress reactivity, reactivity hypothesis

INTRODUCTION

Cardiovascular disease (CVD) and premature mortality remain critical public health concerns¹ and acute psychological stress is an important risk factor for both^{1,2}. Central to understanding the link between stress and CVD/mortality is “stress reactivity”, the cascade of multi-system biological responses (e.g., blood pressure, cortisol) that evolved to enhance survival/coping when facing acute psychological stressors^{1,2}. Although stress reactivity is relatively stable within individuals over many years³, substantial between-individual variability exists^{4,5}. When frequently mounted over time, dysregulated reactivity—whether exaggerated (e.g., by contributing to biological wear and tear) or blunted (e.g., via chronotropic incompetence and links to CVD risk factors that may reflect deficits in motivational and behavioural dysregulation)—is associated with subclinical CVD risk^{6–8}. However, the relationship between dysregulated stress reactivity and clinical CVD risk and mortality remains less well understood, particularly when considering both exaggerated and blunted responses, as well as non-cardiovascular biomarkers.

It also remains unclear whether the strength of associations between stress reactivity and CVD/mortality differs across groups that are disproportionately exposed to acute psychological stress. Addressing this knowledge gap is essential for identifying high-risk populations and developing targeted interventions to reduce health disparities. Notably, racial and ethnic disparities in CVD incidence and premature all-cause mortality have widened across recent decades, with Black and other minoritized populations facing disproportionately greater increases in risk⁹. Findings from the Multi-Ethnic Study of Atherosclerosis (MESA) indicate that Black individuals have a 121% higher risk of hypertension and a 72% increased risk of CVD mortality, compared to White individuals¹⁰. Compared to the racial/ethnic majority, racial and ethnic minorities experience higher exposure to acute stressors¹¹ and have been shown to have dysregulated psychobiological stress reactivity^{13–17}. Thus, and aligned with the Weathering Hypothesis^{17,18}, repeated dysregulated psychobiological reactivity to acute psychological stress represents a plausible, yet understudied, psychobiological mechanism that might drive racial/ethnic inequalities in CVD incidence and premature mortality.

The first aim of this study was to test associations between cardiovascular, cortisol, and sAA reactivity to acute psychological stress and 8-year CVD incidence and all-cause mortality risk in adults free of overt CVD at the time of reactivity testing. We hypothesized that exaggerated and blunted stress reactivity, compared to intermediate reactivity, would be associated with an increased risk for CVD and premature all-cause mortality. The second aim was to investigate whether these associations varied by race/ethnicity, focusing on non-Hispanic White, non-Hispanic Black, and Hispanic individuals. We hypothesized that harmful associations between dysregulated stress reactivity and CVD/mortality would be stronger and more consistent among Black and Hispanic populations.

METHODS

This manuscript followed STROBE reporting guidelines. For full details of the methods, refer to Supplementary Material 1 and ¹⁹.

Study population

The MESA is an ongoing prospective cohort study. Between July 2000 and August 2002, 6,814 men and women aged 45-84 years were recruited from six US urban and suburban communities. The diverse cohort (38% White, 28% Black, 22% Hispanic, 12% Chinese) has completed six follow-up visits and annual interviews. Institutional review boards approved the study at each site, and all participants provided written informed consent.

This analysis involved 1,040 participants (non-Hispanic white, non-Hispanic black, and Hispanic, aged 54–93 years) who completed the MESA stress II ancillary component, which occurred between 2010–2012 (exam 5). After excluding those with CVD prior to stress reactivity assessment, the final sample was N=957.

Stress task protocol

Participants abstained from exercise, food, caffeine, and tobacco for 1 hour, with stress reactivity testing occurring between 11:00-18:00. The stress protocol, detailed previously^{20,21}, included an 11-minute resting baseline, two 6-minute psychological stress tasks (Morgan and Turner Hewitt mental arithmetic

task and Stroop colour word task), each followed by a 6-minute recovery period. Task order was randomized, and participants entered responses via a computer keypad. To induce social evaluation, participants were informed that their performance would be evaluated. The difficulty of both tasks was continuously adjusted based on performance. Participants rated psychological stress (0-7) before and after each task.

Cardiovascular measures

Continuous cardiovascular data were analysed in 300-second epochs. Beat-to-beat blood pressure (BP) was recorded using a Nexfin monitor and finger cuff, with a brachial cuff for calibration. Custom software was used for analysis with manual correction via interpolation.

Electrocardiogram recordings assessed heart rate and heart rate variability (HRV) via 3-lead electrodes placed on the shoulders and torso. R-wave errors were manually corrected. HRV was quantified using time-domain (RMSSD) and frequency-domain (LF-HRV [0.04–0.15 Hz], HF-HRV [0.15–0.50 Hz]) measures, analysed via Fourier transform. The HRV variables were natural log transformed due to severely skewed distributions. In accordance with current recommendations, HRV was not adjusted for respiration as this can reduce variability associated with neural control of the heart^{22,23}.

Neuroendocrine measures

Saliva samples were collected pre-stress and 38 min post-stress using Salivette tubes. Samples were stored at –20°C, thawed, and centrifuged before analysis. Salivary alpha-amylase (sAA) was analysed using an enzyme kinetic method (intra-assay CV <8%; inter-assay CV <12%). Cortisol was measured via a chemiluminescence assay (intra-/inter-assay CV <8%).

Cardiovascular disease incidence and all-cause mortality

The follow-up for clinical events is ongoing and methods have been previously described¹⁹. For this analysis, event ascertainment occurred through December 31, 2019. Only the first recorded event was included in analyses. The primary outcome was incident CVD (myocardial infarction [MI], resuscitated cardiac arrest, definite or probable angina, stroke, stroke death, definite or probable heart failure, coronary heart disease death, other atherosclerotic death, or other CVD-related death. For all-cause mortality

(secondary outcome), deaths were classified by the underlying cause on death certificates, with data obtained from state vital statistics offices and the National Death Index. The large number of “pending adjudication” reasons for mortality precluded CVD mortality analyses.

Covariates

Standard questionnaires and methods¹⁹ were used to collect age (continuous; years), biological sex (male/female), race/ethnicity (self-reported: non-Hispanic White; non-Hispanic Black; Hispanic), bioelectrical impedance-measured total body fat (continuous; kg), low density lipoprotein cholesterol (LDL-C; continuous; mg/dL), moderate-to-vigorous physical activity (MVPA) time (Typical Week Physical Activity Survey; continuous; met-min/week), MESA site for reactivity testing (New York, California, or Maryland), annual income (<\$24,999; \$25,000-\$49,999; \$50,000-\$99,999; >\$100,000), highest education achieved (less than high school; completed high school; some college; college or higher education), cigarette smoking status (never; former; current), current use of alcohol (no/yes), diabetes status (2003 American Diabetes Association fasting criteria; normal; impaired fasting glucose; untreated diabetes; treated diabetes), beta blocker use (no/yes), anti-hypertensive medication use (no/yes), lipid-lowering medication use (no/yes), time of baseline saliva collection (continuous), mean self-reported perceived stress levels across the two stress tasks (scale of 1-10, higher scores indicating higher stress; continuous), and the appropriate resting baseline reference value used to calculate each respective stress reactivity variable (continuous). These covariates were collected at exam 5 unless noted and were selected *a priori* based on established links with stress reactivity and/or CVD/mortality^{5,7,8,10,24,25}.

Statistical analysis

Data were analysed in SAS (version 9.4) with alpha set to $p < 0.05$. Assumptions were checked for all statistical tests. Multiple imputation (10 datasets, Rubin’s Rules) addressed missing exposure, covariate and outcome data. Cardiovascular data were averaged across both stress tasks. Separate repeated measures ANOVAs (2 time points; baseline, stress) confirmed the stress task perturbed psychobiological measures. Stress reactivity was calculated as average stress minus average baseline (the sample collected 38 min post stress minus baseline sample for cortisol and sAA). Reactivity outliers were winsorised

(1st/99th percentile). In the absence of standard clinical cutoffs, we followed prior studies^{5,8,26}, and categorized reactivity variables into high ($\geq 75^{\text{th}}$ percentile), intermediate (26th–74th percentile, reference), and low ($\leq 25^{\text{th}}$ percentile) groups (raw cutoff thresholds are shown for each reactivity variable in Supplementary Material 3). The 25/75th percentile approach was selected over the 33% tertile method to align with similar prior research²⁶, more meaningfully distinguish extreme reactivity, and better capture potential non-linear associations. As HRV measures usually decrease rather than increase in response to stress, we reversed the classification of HRV reactivity groups.

Separate Cox proportional hazard ratio models assessed each stress reactivity variable in relation to CVD (primary outcome), all-cause mortality (secondary outcome), and CVA and CHD (tertiary outcomes).

Each reactivity and outcome variable were first examined in an unadjusted model and then multivariable-adjusted model with all *a priori*-selected covariates entered simultaneously (time of saliva collection was only included in cortisol/sAA models). Kaplan-Meier models visualized reactivity associations with CVD and mortality. To test effect modification by race/ethnicity, an interaction term (race/ethnicity*reactivity) was included in each Cox model.

Finally, we conducted sensitivity analyses comparing our findings to those derived from (1) the 33% reactivity tertile approach and (2) the non-imputed dataset. We also reweighted our analytic sample to the MESA baseline sample using inverse probability of selection weights (IPSW) for our primary (SBP reactivity and CVD incidence) Cox model.

RESULTS

Participant characteristics

This analysis included 957 CVD-free adults. The distribution of demographic and clinical characteristics varied across stress reactivity (shown for SBP reactivity [primary exposure variable] in Table 1). The number of missing data for each variable are reported in Supplementary Material 2.

Table 1. Participant characteristics according to systolic blood pressure stress reactivity group (primary exposure variable).

Characteristic	Total sample n=957	High SBP reactivity n=199	Intermediate (ref) SBP reactivity n=390	Low SBP reactivity n=207
Age (years)	69.1 (9.0)	70.0 (8.6)	67.8 (8.6)	66.5 (8.4)
Sex				
<i>Male</i>	423 (44.2)	83 (41.7)	178 (45.6)	78 (37.7)
<i>Female</i>	534 (55.8)	116 (58.3)	212 (54.4)	129 (62.3)
Race/Ethnicity				
<i>Non-Hispanic White</i>	262 (27.4)	57 (28.6)	110 (28.2)	50 (24.2)
<i>Non-Hispanic Black</i>	301 (31.5)	67 (33.7)	103 (26.4)	71 (34.3)
<i>Hispanic</i>	394 (41.2)	75 (37.7)	177 (45.4)	86 (41.6)
BMI (kg/m²)	29.3 (5.6)	28.5 (5.1)	29.3 (5.5)	30.3 (6.1)
Total Body Fat (kg)	26.1 (11.0)	25.3 (10.5)	25.9 (10.6)	27.5 (12.0)
LDL-C (mg/dL)	107.7 (32.8)	113.1 (35.6)	108.3 (30.2)	108.2 (34.9)
MVPA (met-min/week)	5337 (6785)	4893 (4851)	5475 (6303)	6363 (10028)
Annual Income				
<\$24,999	300 (32.0)	68 (34.2)	112 (28.7)	63 (30.4)
\$25-49,999	275 (29.4)	56 (28.1)	120 (30.8)	57 (27.5)
\$50-99,999	322 (34.4)	65 (32.7)	132 (33.9)	76 (36.7)
>\$100,000	40 (4.3)	7 (3.5)	19 (4.9)	6 (2.9)
Missing		3 (1.5)	7 (1.8)	5 (2.4)
Education				
<i>Less than high school</i>	177 (18.6)	39 (19.6)	70 (18.0)	36 (17.4)
<i>Completed high school</i>	197 (20.7)	36 (18.1)	79 (20.3)	41 (19.8)
<i>Some college</i>	232 (24.4)	50 (25.1)	97 (24.9)	55 (26.6)
<i>College/higher education</i>	346 (36.3)	74 (37.2)	141 (36.2)	73 (35.3)
Missing		0 (0)	3 (0.8)	2 (1.0)
Cigarette Smoking Status				
<i>Never</i>	446 (46.6)	94 (47.2)	190 (48.7)	93 (44.9)
<i>Former</i>	451 (47.1)	94 (47.2)	176 (45.1)	95 (45.9)
<i>Current</i>	60 (6.3)	11 (5.5)	24 (6.2)	19 (9.2)
Alcohol: Current Use				
<i>No</i>	581 (61.0)	114 (57.3)	247 (63.3)	129 (62.3)
<i>Yes</i>	371 (39.0)	85 (42.7)	143 (36.7)	76 (37.7)
Missing		0 (0)	0 (0)	2 (1.0)
Diabetes (2003 ADA Fasting Criteria)				
<i>Normal</i>	571 (60.0)	129 (64.8)	244 (62.6)	111 (53.6)
<i>IFG</i>	187 (19.7)	42 (21.1)	75 (19.2)	32 (15.5)
<i>Untreated diabetes</i>	12 (1.3)	1 (0.5)	7 (1.8)	4 (1.9)

<i>Treated diabetes</i>	181 (19.0)	26 (13.1)	62 (15.9)	58 (28.0)
<i>Missing</i>		1 (0.5)	2 (0.5)	2 (1.0)
Beta-blockers without diuretics				
<i>NO</i>	796 (83.2)	166 (83.4)	324 (83.1)	180 (89.0)
<i>YES</i>	161 (16.8)	33 (16.6)	66 (16.9)	27 (13.0)
Any Anti-hypertensive Medication				
<i>NO</i>	410 (42.8)	90 (45.2)	176 (45.1)	90 (43.5)
<i>YES</i>	547 (57.2)	109 (54.8)	214 (54.9)	117 (56.5)
Any Lipid-lowering Medication				
<i>NO</i>	602 (62.9)	125 (62.8)	244 (65.6)	135 (65.2)
<i>YES</i>	355 (37.1)	74 (37.2)	146 (37.4)	72 (34.8)

Note: Characteristics are mean (standard deviation) or counts (percentage). SBP = systolic blood pressure; BMI = body mass index; MVPA = moderate-to-vigorous physical activity; LDL-C = low-density lipoprotein-cholesterol; ADA= American Diabetes Association; IFG = impaired fasting glucose. Data for the SBP reactivity groups reflects non-imputed data, such that individuals with missing SBP reactivity data were not categorized to an exposure group, which is the reason for differences in group sample size relative to total sample size. High reactivity ($\geq 75^{\text{th}}$ percentile), intermediate reactivity ($26^{\text{th}}-74^{\text{th}}$ percentile, reference group), and low reactivity ($\leq 25^{\text{th}}$ percentile).

Follow-up time and number of clinical events

The median follow-up was 7.9 ± 1.1 years for CVD incidence, 8.0 ± 1.0 years for all-cause mortality, 7.9 ± 1.0 years for CVA incidence, and 7.9 ± 1.0 years for CHD incidence. During follow-up, 111 (11.6%) participants experienced CVD, 114 (11.9%) died, 45 (4.7%) had CHD, and 42 (4.4%) had CVA.

Psychobiological responses to the stress protocol

All biological parameters showed significant responses to the stress protocol (all $p < .001$; Table 2). Self-reported stress levels increased ($p < .001$, $\eta^2 = 0.51$) from pre-stress resting baseline (2.5 ± 1.8) to during the stress protocol (4.3 ± 2.0). Correlations among stress reactivity variables and self-reported stress are shown in Supplementary Material 4.

Table 2. Biological responses to the psychological stress protocol.

Measure	Total or reactivity group	Baseline	Stress	Stress reactivity (Δ)	Effect size (η^2)
SBP reactivity	Total n=957	129.7 (19.7)	145.6 (21.8)	16.0 (12.3)	0.63
	Low n=252	133.5 (21.3)	134.7 (20.5)	1.1 (8.9)	
	Int n=465	128.0 (19.2)	143.9 (19.5)	15.9 (4.4)	
	High n=240	129.4 (19.2)	160.7 (19.1)	31.3 (7.1)	
DBP reactivity	Total n=957	64.9 (8.4)	71.4 (9.4)	6.4 (4.8)	0.63
	Low n=253	65.9 (8.6)	66.5 (8.8)	0.6 (3.6)	
	Int n=461	64.7 (8.1)	71.1 (8.3)	6.5 (1.7)	
	High n=243	64.5 (8.5)	76.8 (8.3)	12.3 (2.5)	
Heart rate reactivity	Total n=957	68.5 (10.6)	71.6 (11.0)	3.1 (3.9)	0.39
	Low n=250	69.8 (12.0)	68.7 (11.9)	-1.0 (2.5)	
	Int n=457	68.0 (10.17)	70.8 (10.3)	2.8 (1.1)	
	High n=250	67.1 (10.2)	75.1 (10.7)	8.1 (3.2)	
RMSSD reactivity	Total n=957	3.0 (0.6)	2.9 (0.6)	-0.1 (0.4)	0.07
	High n=256	3.2 (0.6)	2.7 (0.6)	-0.5 (0.3)	
	Int n=469	2.9 (0.6)	2.8 (0.6)	-0.10 (0.1)	
	Low n=232	2.8 (0.6)	3.1 (0.6)	0.3 (0.2)	
LF-HRV reactivity	Total n=957	5.1 (1.2)	4.5 (1.1)	-0.6 (0.8)	0.30
	High n=247	5.7 (1.0)	4.1 (1.0)	-1.6 (0.5)	
	Int n=469	5.1 (1.0)	4.5 (1.0)	-0.5 (0.3)	
	Low n=241	4.4 (1.1)	4.9 (1.0)	0.5 (0.4)	
HF-HRV reactivity	Total n=957	4.7 (1.3)	4.4 (1.3)	-0.4 (0.8)	0.17
	high n=256	5.2 (1.2)	3.8 (1.2)	-1.4 (0.5)	
	Int n=474	4.7 (1.3)	4.4 (1.3)	-0.3 (0.2)	
	Low n=227	4.3 (1.3)	4.9 (1.2)	0.6 (0.5)	
sAA reactivity	Total n=957	131.2 (136.8)	139.4 (130.8)	8.2 (80.2)	0.01
	Low n=246	223.3 (169.9)	149.3 (140.3)	-74.1 (77.2)	
	Int n=466	78.9 (89.6)	85.0 (86.9)	6.2 (17.4)	
	High n=245	137.1 (119.9)	231.5 (135.0)	94.4 (67.6)	
Cortisol reactivity	Total n=957	8.7 (5.4)	9.5 (6.4)	0.8 (4.6)	0.03
	Low n=251	12.5 (5.6)	9.2 (5.5)	-3.4 (2.8)	
	Int n=468	6.7 (4.3)	7.0 (4.6)	0.3 (1.1)	
	High n=238	8.3 (4.7)	14.8 (7.1)	6.5 (4.7)	

Note: Data are presented as mean (SD). High reactivity ($\geq 75^{\text{th}}$ percentile), intermediate reactivity (26^{th} – 74^{th} percentile, reference group), and low reactivity ($\leq 25^{\text{th}}$ percentile). Int = intermediate; SBP = systolic blood pressure; DBP = diastolic blood pressure; RMSSD = root mean square of successive differences; LF-HRV = low frequency heart rate variability; HF-HRV = high frequency heart rate variability, sAA = salivary alpha amylase. Reactivity refers to change from baseline to during stress (from baseline to 38 minutes post-baseline for SAA and cortisol). Note, all time effects were significant at $p < .001$. HRV reactivity groups were reversed to align with other physiological measures; a larger HRV decrease in

response to stress was classified as ‘high’ reactivity. Effect size represents the magnitude of change from baseline to stress across the whole sample, with η^2 values interpreted as small (≥ 0.01), medium (≥ 0.06), and large (≥ 0.14) effects.

Psychobiological stress reactivity and incident cardiovascular disease

Cox proportional hazard ratio models

In adjusted models, the overall main effect for all stress reactivity variables with incident CVD were non-significant (Table 3); individuals with high ($p \geq .287$) or low ($p \geq .246$) stress reactivity did not have a higher risk of incident CVD compared to the respective intermediate group.

Table 3. Hazard ratios for stress reactivity exposure variables and cardiovascular disease incidence.

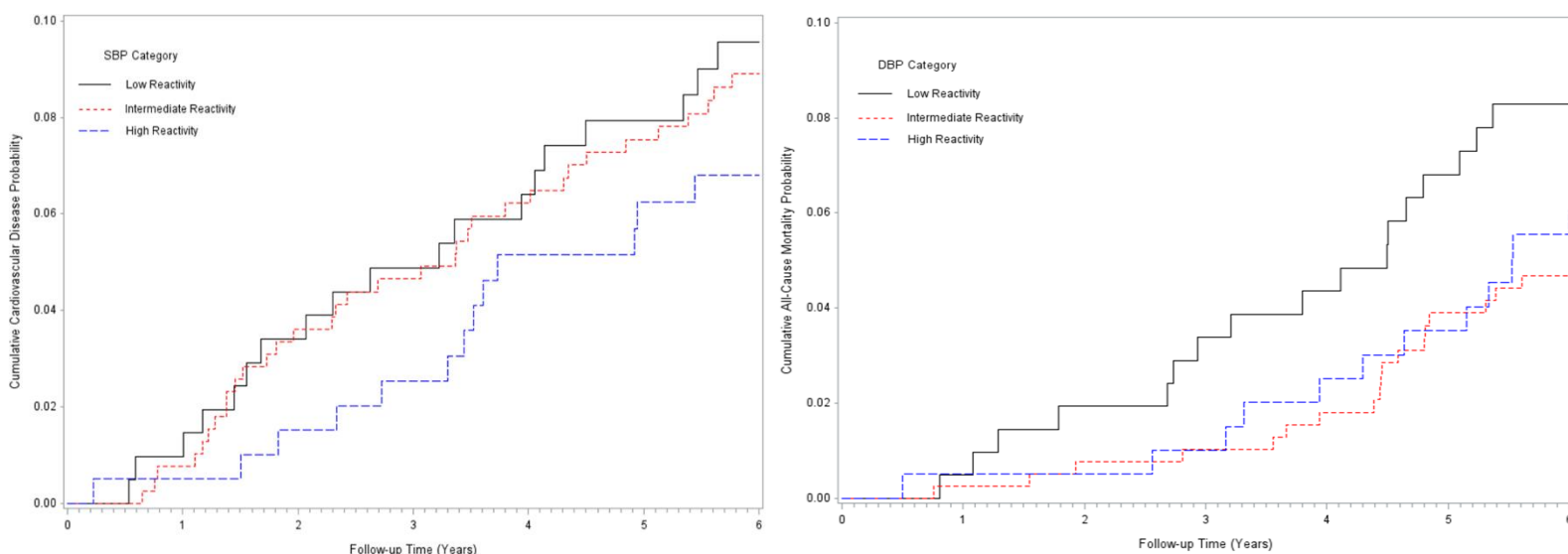
Variable	Reactivity group	Events / censored / mean person-years	Unadjusted HR (95% CI)	Adjusted HR (95% CI)	Wald χ^2 (p)
SBP reactivity	High	32 / 236 / 5.31	1.06 (0.64, 1.75)	1.01 (0.59, 1.71)	0.54 (.787)
	Int	49 / 384 / 8.71	Reference	Reference	
	Low	30 / 226 / 4.90	1.09 (0.65, 1.81)	1.06 (0.62, 1.81)	
DBP reactivity	High	32 / 234 / 5.38	1.20 (0.72, 2.00)	1.17 (0.69, 2.00)	2.21 (.383)
	Int	43 / 389 / 8.64	Reference	Reference	
	Low	35 / 223 / 4.90	1.43 (0.89, 2.32)	1.36 (0.81, 2.27)	
Heart rate reactivity	High	28 / 264 / 5.87	0.83 (0.49, 1.39)	0.86 (0.50, 1.47)	2.83 (.365)
	Int	48 / 370 / 8.33	Reference	Reference	
	Low	34 / 213 / 4.72	1.25 (0.76, 2.05)	1.26 (0.75, 2.12)	
RMSSD reactivity	High	31 / 263 / 5.87	0.90 (0.54, 1.51)	0.85 (0.49, 1.48)	1.24 (.598)
	Int	47 / 358 / 7.98	Reference	Reference	
	Low	33 / 225 / 5.08	1.08 (0.64, 1.83)	0.96 (0.55, 1.67)	
LF-HRV reactivity	High	28 / 247 / 5.46	0.96 (0.55, 1.68)	0.96 (0.55, 1.68)	2.33 (.371)
	Int	46 / 382 / 8.53	Reference	Reference	
	Low	37 / 217 / 4.94	1.41 (0.87, 2.28)	1.33 (0.78, 2.28)	
HF-HRV reactivity	High	35 / 247 / 5.61	1.19 (0.72, 1.95)	1.12 (0.65, 1.94)	1.40 (.547)
	Int	44 / 377 / 8.34	Reference	Reference	
	Low	32 / 223 / 4.98	1.23 (0.65, 2.32)	1.13 (0.59, 2.19)	
sAA reactivity	High	37 / 229 / 5.35	1.36 (0.87, 2.13)	1.09 (0.68, 1.74)	0.73 (.706)
	Int	44 / 394 / 8.60	Reference	Reference	
	Low	30 / 223 / 5.00	1.17 (0.72, 1.88)	0.88 (0.51, 1.54)	
Cortisol reactivity	High	33 / 218 / 4.90	1.16 (0.75, 1.79)	1.27 (0.81, 2.00)	2.22 (.335)
	Int	53 / 407 / 9.21	Reference	Reference	
	Low	25 / 221 / 4.82	0.90 (0.56, 1.46)	0.85 (0.52, 1.41)	

Note: High reactivity ($\geq 75^{\text{th}}$ percentile), intermediate reactivity ($26^{\text{th}}-74^{\text{th}}$ percentile, reference group), and low reactivity ($\leq 25^{\text{th}}$ percentile). Int = intermediate; HR = hazard ratio; SBP = systolic blood pressure; DBP = diastolic blood pressure; RMSSD = root mean square of successive differences; LF-HRV = low frequency heart rate variability; HF-HRV = high frequency heart rate variability, sAA = salivary alpha

amylase. Reactivity refers to change from baseline to during stress (from baseline to 38 minutes post-baseline for SAA and cortisol). Wald χ^2 (p) reflects overall model statistics.

Kaplan-Meier models

Figure 1 displays the Kaplan-Meier curve for our primary exposure (SBP reactivity) and outcome (CVD incidence) data; the remaining Kaplan-Meier curves are found in Supplementary Material 6. The log-rank test did not support statistical differences in CVD incidence for SBP or any other reactivity variable (all Wald $\chi^2(2)$ p -values >0.05).



SBP reactivity	Year 0	Year 2	Year 4	Year 6
Low	208	197	183	167
Int	390	370	353	332
High	200	194	179	168

DBP reactivity	Year 0	Year 2	Year 4	Year 6
Low	208	203	195	185
Int	391	385	377	362
High	200	198	194	186

Figure 1. Kaplan-Meier survival data for CVD incidence (by SBP reactivity group) and all-cause mortality (by DBP reactivity group). *Note:* Data in tables represents numbers at risk across time. High reactivity (≥ 75 th percentile), intermediate reactivity (26th–74th percentile, reference group), and low reactivity (≤ 25 th percentile).

Psychobiological stress reactivity and all-cause mortality

Cox proportional hazard ratio models

In adjusted models, DBP (Wald $\chi^2(2)=8.55$, $p=.045$) and sAA (Wald $\chi^2(2)=8.117$, $p=.020$) reactivity were associated with all-cause mortality. Those with low ($p=.040$), but not high ($p=.186$) DBP reactivity had a higher risk of all-cause mortality compared to the intermediate DBP reactivity group (Table 4). For sAA,

individuals with high ($p=.042$) and low ($p=.017$) reactivity had a lower risk of all-cause mortality compared to the intermediate sAA reactivity group. The remaining stress reactivity variables were not associated with all-cause mortality (all *Wald* $\chi^2(2)$ p -values >0.05), such that individuals with high ($p\geq.274$) and low ($p\geq.312$) reactivity did not have a higher risk compared to the respective intermediate category.

Table 4. Hazard ratios for stress reactivity exposure variables and all-cause mortality.

Variable	Reactivity group	Events / censored / Mean Person-years	Unadjusted <i>HR</i> (95% CI)	Adjusted <i>HR</i> (95% CI)	<i>Wald</i> χ^2 (p)
SBP reactivity	High	37 / 231 / 5.64	1.39 (0.83, 2.34)	1.13 (0.67, 1.91)	2.12 (.462)
	Int	44 / 389 / 9.30	Reference	Reference	
	Low	33 / 223 / 5.27	1.33 (0.77, 2.29)	1.35 (0.75, 2.46)	
DBP reactivity	High	36 / 230 / 5.69	1.56 (0.93, 2.62)	1.40 (0.85, 2.35)	8.55 (.045)
	Int	38 / 395 / 9.22	Reference	Reference	
	Low	40 / 219 / 5.30	1.85 (1.06, 3.20)	1.92 (1.03, 3.56)	
Heart rate reactivity	High	39 / 253 / 6.20	1.32 (0.80, 2.17)	1.33 (0.80, 2.20)	2.33 (.368)
	Int	43 / 376 / 8.94	Reference	Reference	
	Low	32 / 215 / 5.07	1.33 (0.82, 2.18)	1.28 (0.77, 2.13)	
RMSSD reactivity	High	43 / 252 / 6.22	1.56 (0.96, 2.56)	1.31 (0.77, 2.26)	2.23 (.406)
	Int	38 / 367 / 8.59	Reference	Reference	
	Low	34 / 224 / 5.40	1.42 (0.77, 2.62)	1.20 (0.63, 2.30)	
LF-HRV reactivity	High	38 / 238 / 5.75	1.22 (0.74, 1.20)	1.37 (0.73, 2.54)	4.53 (.710)
	Int	49 / 378 / 9.09	Reference	Reference	
	Low	27 / 227 / 5.36	0.92 (0.54, 1.57)	0.79 (0.46, 1.35)	
HF-HRV reactivity	High	38 / 244 / 5.97	1.28 (0.80, 2.07)	1.22 (0.66, 1.88)	1.14 (.650)
	Int	44 / 376 / 8.89	Reference	Reference	
	Low	32 / 223 / 5.34	1.20 (0.67, 2.17)	0.97 (0.53, 1.81)	
sAA reactivity	High	26 / 240 / 5.72	0.70 (0.43, 1.13)	0.58 (0.35, 0.98)	8.12 (.020)
	Int	59 / 379 / 9.14	Reference	Reference	
	Low	29 / 224 / 5.34	0.82 (0.52, 1.31)	0.52 (0.30, 0.89)	
Cortisol reactivity	High	29 / 222 / 5.24	1.08 (0.68, 1.72)	1.06 (0.65, 1.74)	0.32 (.856)
	Int	50 / 410 / 9.78	Reference	Reference	
	Low	35 / 211 / 5.18	1.34 (0.86, 2.08)	1.12 (0.71, 1.77)	

Note: High reactivity (≥ 75 th percentile), intermediate reactivity (26th–74th percentile, reference group), and low reactivity (≤ 25 th percentile). Int = intermediate; SBP = systolic blood pressure; DBP = diastolic blood pressure; RMSSD = root mean square of successive differences; LF-HRV = low frequency heart rate variability; HF-HRV = high frequency heart rate variability, sAA = salivary alpha amylase.

Reactivity refers to change from baseline to during stress (from baseline to 38 minutes post-baseline for SAA and cortisol). *Wald* χ^2 (p) reflects overall model statistics, bold text indicates significant ($p < 0.05$) overall model effect.

Kaplan-Meier models

As shown in Figure 2, all-cause mortality rates differed by DBP reactivity group (*Wald* $\chi^2(2)$ p -value=.048). Mortality risk was statistically greater in adults with low vs. intermediate (p =.018), but not high vs intermediate (p =.055) DBP reactivity. There were no differences in all-cause mortality risk across the remaining stress reactivity exposure variables (all *Wald* $\chi^2(2)$ p -values >0.05); the associated Kaplan-Meier curves are displayed in Supplementary Material 7.

Effect modification by race/ethnicity for CVD incidence and all-cause mortality

We did not observe evidence to support differential associations by race/ethnicity for any stress reactivity measure with CVD incidence or all-cause mortality (all p -for-interaction>0.05). Supplementary Table 5 presents findings stratified by race/ethnicity.

Supplementary analyses

The data linking stress reactivity to CVD and CHD are available in Supplementary Material 8.

Sensitivity analyses

The mean IPSW was 1.0026 (SD=0.0522). In the covariate-adjusted model without IPSW, the HR was 1.010 (95% CI: 0.593–1.713, p =.976) for high versus intermediate SBP reactivity and 1.060 (95% CI: 0.621–1.813, p =.828) for low versus intermediate SBP reactivity. With IPSW adjustment, these HRs became 1.014 (95% CI: 0.598–1.721, p =.956) and 1.068 (95% CI: 0.628–1.818, p =.805), respectively. In addition, our findings were largely consistent when derived from the 33% reactivity tertile approach and the non-imputed dataset.

DISCUSSION

This study examined whether exaggerated or blunted psychobiological reactivity to acute psychological stress predicted 8-year CVD incidence and all-cause mortality in initially CVD-free adults. No significant associations were found for CVD risk. Blunted DBP reactivity was linked to increased mortality risk, whereas both exaggerated and blunted sAA reactivity were associated with reduced mortality risk. No statistical effect modification by race/ethnicity was observed.

Acute psychobiological stress reactivity and cardiovascular disease incidence

Our findings contrast with prior research linking exaggerated and blunted SBP, DBP, heart rate, and cortisol stress reactivity with subclinical and clinical CVD risk^{7,8,27}. Possible explanations include the modest follow-up duration (~8 years) and that our study population was initially free from overt CVD, whereas previous research has found stronger associations in individuals with pre-existing disease or higher risk profiles²⁷. Supporting this, our results align with other studies that have similarly found no relationship between stress reactivity and risk of 10-year clinical CVD events in initially CVD-free individuals²⁸. It is possible that robust regulatory mechanisms—such as autonomic flexibility and vascular resilience—may help buffer against the adverse effects of dysregulated stress reactivity in healthy populations^{1,2,27,28}. Overall, our findings, based on a relatively large sample (N=957), question whether stress reactivity is associated with CVD incidence in disease-free populations^{27,28}, and we extend this literature by demonstrating this null association with additional stress reactivity measures, including HRV and sAA.

Acute psychobiological stress reactivity and all-cause mortality

Blunted DBP reactivity was associated with a 92% higher risk of all-cause mortality, independent of resting DBP and covariates. This suggests that DBP reactivity has unique prognostic value beyond resting DBP, potentially due to different genetic underpinnings²⁹. Possible mechanisms linking blunted DBP reactivity to mortality need to be directly tested, but may involve links with CVD risk factors, such as depression and adiposity^{7,8}, and motivational dysregulation, including reduced engagement in health-promoting behaviours such as physical activity and medical adherence^{5,7,25,30}. To our knowledge, this study is the first to demonstrate that blunted DBP reactivity may serve as a marker of all-cause mortality risk among disease-free individuals, building on prior research in heart failure^{26,31} and acute coronary syndrome³² patients. Our study contributes to the growing body of literature suggesting that blunted DBP reactivity, in particular, may be an especially relevant risk factor for all-cause mortality.

Unexpectedly, both high and low sAA responses to stress were associated with lower risk of all-cause mortality. The link between sAA reactivity and future subclinical or clinical disease has been largely

unexplored⁸, which is a novel and important aspect of this present study. Our findings for sAA reactivity and mortality challenge the widely accepted assumption that moderate psychobiological responses to stress are always the most desirable^{5,8}. One speculative explanation is that a moderate sAA response reflects ineffective stress and autonomic regulation, where the body neither fully mobilizes resources to cope nor conserves energy for recovery. However, it is not clear why this effect would only be apparent for sAA reactivity rather than across all biological stress responses. Further research is clearly needed.

Effect modification by race/ethnicity

Our analyses suggest that relationships between stress reactivity and CVD/mortality are generally consistent across racial/ethnic groups. Race/ethnicity effect modification was tested because various psychosocial, structural, and environmental factors (e.g., discrimination, acculturation stress, healthcare access, disparities in coping and health behaviours) aligned the Weathering Hypothesis¹⁷, may drive racial/ethnic disparities in CVD and mortality by exacerbating the effects of acute stress and reactivity dysregulation^{18,33,34}. Future studies with confirmed statistical power must verify that race/ethnicity does not modify the reactivity-CVD/mortality link across disease-free and clinical populations.

Methodological considerations

This study has several limitations. The laboratory stress protocol does not reflect real-world stress exposure, limiting ecological validity. The stress tasks likely induced only mild social-evaluative threat, potentially explaining the small (albeit significant) overall cortisol response³⁵. The analysed sample represents a subset of MESA and despite efforts to ensure representativeness, selection bias cannot be ruled out. As an observational study, causality cannot be inferred, and residual confounding may persist despite extensive covariate adjustment. Generalizability is limited as Chinese American MESA participants were not enrolled at sites offering the stress reactivity protocol. Analyses were conducted on reactivity categories for interpretability, but this may have reduced statistical power. Finally, we did not apply multiple testing corrections, so caution is warranted regarding the potential for Type I error. This decision was made because our analyses were hypothesis-driven and preplanned, and standard correction

methods—assuming independent tests—might have been overly conservative given the interdependence of stress reactivity measures, thereby increasing the risk of Type II error.

Our study also has many strengths. First, it leverages a large, well-characterized prospective cohort with rigorous protocols for data collection and clinical event adjudication, along with considerable racial/ethnic diversity. Second, the inclusion of multiple biological stress markers provided a comprehensive, multisystem assessment of stress reactivity. Lastly, statistical approaches were employed to account for selective attrition.

Future directions

Future studies should expand to other underrepresented groups (e.g., Asian and Indigenous populations), and consider additional biomarkers (e.g., inflammatory, vascular, neural), stress tasks (e.g., more ecologically valid tasks, active vs. passive tasks), and response patterns (e.g., recovery, habituation). Later work could use clustering to assess stress reactivity across multiple biological systems³⁶ or ecological momentary assessment and wearable devices to capture reactivity to real-world, naturalistic stressors.

Conclusions

Among adults free from CVD at the time of reactivity testing, no significant associations emerged between dysregulated stress reactivity and 8-year CVD incidence. Both exaggerated and blunted sAA reactivity were associated with reduced risk of all-cause mortality, whereas blunted DBP reactivity predicted increased mortality risk. Race/ethnicity was not an effect modifier between stress reactivity and CVD incidence or all-cause mortality. Although standardized testing protocols and established reference values are necessary, these findings highlight the potential value of integrating stress physiology into public health strategies, including targeted interventions for blunted DBP reactivity to help prevent premature mortality.

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CONFLICT OF INTEREST

The authors have no conflicts to disclose. The views expressed in this manuscript are those of the authors and do not necessarily represent the views of the National Heart, Lung, and Blood Institute; the National Eye Institute; the National Institutes of Health; or the U.S. Department of Health and Human Services.

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AUTHOR CONTRIBUTIONS

Dr. Chantry is the guarantor of this work. As such, he takes responsibility for the integrity of the data and the accuracy of the data analysis and affirms that the manuscript is an honest, accurate, and transparent account of the study being reported. All authors made substantial intellectual contributions participating in creating and designing the study, analysing and interpreting the data, and reviewing this manuscript. All authors have read and approved the final report for publication.

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