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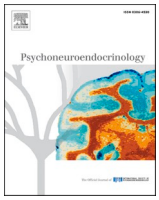

The association between cardiac vagal activity and urinary catecholamine: Investigating the effect of race and sex

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ABSTRACT

Black individuals are at greater risk for the development of cardiovascular diseases compared to White individuals. Autonomic nervous system (ANS) dysregulation has been identified as a significant risk factor contributing to racial disparities in cardiovascular disease, yet systematic racial differences that affect the measurement of ANS activity among White and Black participants are likely obscuring understanding about ANS-health disparity links. Moreover, sex differences in ANS activity have been observed. Thus, efforts to elucidate the comparability of ANS indices across race and sex are needed. This study aimed to investigate the effects of race and sex on the associations between two indices of ANS activity—cardiac vagal activity and urinary catecholamines—in a sample of White and Black participants from the MIDUS 2: Biomarker Project (N = 967 adults aged 34 – 84; 81 % White, 57 % female). Participants self-reported their sociodemographic and health information and completed biomarker assessments. Cardiac vagal activity was assessed via heart rate (HR) and heart rate variability (HRV); urinary catecholamines were assessed via epinephrine and norepinephrine. Black participants displayed higher HRV activity and lower levels of urinary catecholamines relative to White participants. Moreover, our results revealed small but significant correlations between urinary catecholamines and cardiac vagal activity across both races, though the nature of these relations varied across race, sex, and ANS index. The correlations between HR and epinephrine and norepinephrine were stronger among Black male participants compared to White male participants. Our results highlight the importance of clarifying the functional equivalence of different ANS indices across race and sex.

1. Introduction

Cardiovascular diseases are the leading causes of death for adults in the United States, with significant racial disparities. Black Americans face higher cardiovascular risk factors, such as hypertension and obesity, and have twice the mortality risk from these diseases compared to White Americans (Javed et al., 2022). Dysregulation of the autonomic nervous system (ANS), a major bodily stress response system, is theorized to contribute to these disparities (Thayer et al., 2010; Hill et al., 2015; Hill and Thayer, 2019). The ANS has two branches: the parasympathetic nervous system (PNS), which promotes "rest and digest" functions, and the sympathetic nervous system (SNS), which activates the "fight or flight" responses. Modest PNS activation and lower SNS activity support health by enhancing physiological adaptability (Thayer and Lane, 2000). In contrast, chronic PNS withdrawal and SNS activation have been linked to higher cardiovascular risk

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(Thayer et al., 2010). Recent research reveals racial differences in ANS activity influencing cardiovascular risks among Black and White participants. Contrary to the expectations of cardiovascular risk correlated with excessively elevated SNS and attenuated PNS in White Americans (Thayer and Lane, 2000), Black Americans exhibit a "cardiovascular conundrum" characterized by both elevated PNS *and* SNS activity (Hill and Thayer, 2019). Understanding the association between these systems is crucial for examining racial disparities in cardiovascular outcomes.

1.1. Racial differences in cardiac vagal activity and SNS activity

Recent studies have highlighted significant racial differences in cardiac vagal activity, particularly between Black and White Americans, which may contribute to differing cardiovascular risk profiles. Specifically, a review by Hill and Thayer (2019) demonstrated that Black Americans consistently exhibit more PNS activity at rest, as indicated by indices such as high-frequency heart rate variability (HF-HRV; an index of heart rate variations related to the respiratory cycle) and root mean square of successive differences between normal heartbeats (RMSSD; an index of vagally mediated changes reflected in HRV) than White Americans. Few studies have focused on low-frequency HRV (LF-HRV; an index of baroreflex activity), which also correlates with PNS activity (Thayer and Lane, 2007). Some suggested that Black participants may have lower LF-HRV than White participants (Choi et al., 2006; Lampert et al., 2005), while others report no differences (Shekh, 2016; Wang et al., 2005). Further research on LF-HRV is needed. These findings suggest that Black participants may experience increased PNS activity, which traditionally associates with better cardiovascular health. However, the literature remains mixed regarding whether this increased PNS activity is linked with improved outcomes or paradoxical effects. Additionally, longitudinal research on heart rate (HR), another cardiac vagal activity that integrates effects of both PNS and SNS, indicated that Black adult men generally experienced an increasing HR trend over 20 years, while Black women and White adults often showed a decreasing HR trend (Colangelo et al., 2020).

Black Americans also show higher resting SNS activity, especially higher resting total peripheral resistance (TPR; an index of blood flow resistance associated with alpha-adrenergic vasoconstriction) than White Americans (Brownlow et al., 2020). Nevertheless, racial differences in SNS activity may depend on the index used (Chong et al., 2023). For example, despite elevated TPR, Black individuals consistently exhibit lower resting electrodermal activity (EDA; an SNS index that measures sweat activity thought to be primarily associated with beta-adrenergic activity), indicating lower SNS activity compared to White participants (Chong et al., 2023). This suggests that Black participants may not display a general systemic SNS elevation across all biological systems, pointing to the complexity of the ANS activity across races (Chong et al., 2023). Thus, researchers are urged to continue explore racial differences in SNS activity using less studied indices, such as catecholamines (Chong et al., 2023).

Catecholamines (e.g., epinephrine and norepinephrine) are neurotransmitters that regulate SNS-related outcomes, including HR, cardiac output, and peripheral resistance. Catecholamines bind to alpha and beta receptors — alpha with higher norepinephrine affinity, and beta with greater epinephrine affinity. Alpha adrenergic activity is associated with vasoconstriction whereas beta adrenergic activity is associated with vasodilation. Higher levels of catecholamines reflect greater SNS activity but with varying effects on cardiovascular activity as a function of the receptors primarily activated. While catecholamines are essential to cardiac function, their dysregulation can exacerbate cardiovascular issues (Xiang et al., 2023). Despite the pivotal role of catecholamines in cardiovascular health, literature on racial differences in resting catecholamine levels remains mixed. Most studies indicate no significant racial differences in resting catecholamine levels between Black and White participants (Blaudeau et al., 2008; Homandberg and Fuller-Rowell, 2020; Reuben et al., 2000; van Berge-Landry et al., 2008; Walker et al., 1992). However, three studies found racial differences: Mills et al. (1995) reported lower resting epinephrine in Black men compared to White men, James (2018) noted higher norepinephrine in Black women compared to White, Asian, Hispanic women, and Masi et al. (2004) found higher overall catecholamine levels in Black participants relative to White participants, with women having higher levels than men. Of note, these studies used relatively small samples and lacked covariate controls, limiting interpretability. Thus, further investigating catecholamines in the context of race and sex is needed.

1.2. Racial differences in ANS coordination

While higher HF-HRV has been found to correlate with lower TPR among White Americans, associations with TPR among Black Americans are less consistent. Williams et al. (2021) found that, among White Americans, higher initial HF-HRV corresponded with lower TPR six years later. In contrast, Black Americans consistently showed elevated resting TPR at both time points, indicating long-term increases that were independent of HF-HRV levels (Williams et al., 2021). This suggests differing PNS-SNS coordination patterns by race, which may underlie cardiovascular disparities. Efforts to clarify the relations between ANS indices across racial groups, particularly for SNS measures like catecholamines, are critical to clarify ANS's role in stress-health links.

The relationship between HRV and catecholamines is inconsistent; some studies find no correlation (Fagundes et al., 2011; Sloan et al., 1996; Vlcek et al., 2008), while others suggest a small inverse relationship (Lee et al., 2010; Thayer and Fischer, 2013). These studies are either conducted using small samples ($n < 40$ for Sloan et al., 1996 and Vlcek et al., 2008) or among specific samples (e.g., Korean male manufacturing workers for Lee et al., 2010; healthy German employees for Thayer and Fischer, 2013; cancer survivors for Fagundes et al., 2011), limiting generalizability. Investigating these associations using a larger, more representative sample, and at the intersections of race and sex, may offer more clarity.

1.3. Sex differences in cardiac vagal activity and catecholamines

Cardiovascular risk differs significantly by sex, with males typically at higher risk than females (Betai et al., 2024). Females often display higher PNS activity (e.g., HF-HRV and LF-HRV) compared to males, which is associated with better cardiovascular outcomes (Koenig and Thayer, 2016). However, sex differences in catecholamine levels remained underexplored and showed mixed results: some studies reported higher catecholamine levels in women (Masi et al., 2004; Reuben et al., 2000), while others found lower levels (Hansen et al., 2001). Given that catecholamines are critical regulators of HR and vascular tone, understanding these discrepancies is crucial for identifying how sex influences the balance between PNS and SNS activity and within ANS activity. Clarifying these dynamics may improve our understanding of sex-specific cardiovascular risk and stress responses.

1.4. Current study

This study had two aims. First, we examined race and sex differences in cardiac vagal activity and catecholamines among middle-aged White and Black female and male participants. Informed by previous findings, we hypothesized that Black participants would display higher HF-HRV and RMSSD, along with lower catecholamines, compared to White participants, with no HR differences expected due to reduced racial differences in middle-aged adults (Colangelo et al., 2020). We predicted that females would display higher levels of HR, HF-HRV, LF-HRV, and catecholamines than males. The second aim was to explore how associations between cardiac vagal activity and catecholamines differ across race and sex. To our knowledge, this is the first study to investigate these associations based on race and sex, with implications for understanding

cardiovascular risk disparities. By addressing the conflicting findings in the literature, this study would clarify the mechanistic role of the ANS in explaining stress-health links, particularly for understudied SNS measures like catecholamines.

2. Methods

2.1. Data, participants, and designs

The Midlife in the United States (MIDUS) study is a longitudinal, nationally representative study that examined the biopsychosocial factors that contribute to age-related health problems (Brim et al., 2004; Radler et al., 2014). We drew data from the MIDUS 2: Biomarker Project, (2004 – 2009) that aimed to examine biological factors that influence health outcomes (Ryff et al., 2022; Ryff and Krueger, 2018). The MIDUS 2: Biomarker Project was conducted at the University of California, Los Angeles, the University of Wisconsin, and Georgetown University. The study protocol was approved by the Institutional Review Boards at each participating site. Information related to participants' psychosocial, sociodemographic, and health functioning was collected via self-report. Participants also provided biomarker assessments via urine, saliva, blood samples, and continuous physiological recordings of heart rate during different experimental protocols (e.g., resting period, arithmetic and cognitive challenges, and recovery from challenges).

The MIDUS 2: Biomarker Project consisted of 1255 participants. We excluded 44 participants who did not complete the cardiac vagal activity data acquisition, 123 participants whose cardiac vagal activity was unscoreable, and 67 participants who did not provide a urine sample. We further excluded seven participants who did not self-report their race/ethnicity and 47 participants who did not self-identify as Black or White (14 Native American or Native Alaskan participants; three Asian participants; 30 "Other" participants) due to insufficient sample size in each racial/ethnic group. Thus, our final analytic sample included 967 adults, including 785 White participants (M_{age} = 55.63; SD_{age} = 11.86; 55 % females) and 182 Black participants (M_{age} = 50.74; SD_{age} = 10.57; 66 % females). Black participants were recruited only from Milwaukee, Wisconsin. Demographic and physiological characteristics are presented in Table 1.

2.2. Measures

2.2.1. Baseline cardiac vagal activity

Cardiac vagal activity was assessed using HR and HRV. HRV was further evaluated across both time (i.e., rMSSD) and frequency domain (i.e., LF-HRV and HF-HRV) measures. Details of cardiac vagal activity acquisition and processing are outlined in Ryff et al. (2022) and are also available on the MIDUS website (https://midus.wisc.edu/midus2/project4/). In short, all cardiac vagal activity was measured using an electrocardiograph (ECG) sampled at 500 Hz and digitized at 16 bits. ECG lead electrodes and inductotrace bands were attached to the participant's torso and chest. Participants sat quietly for an 11-minute baseline period while ECG data acquisition was ongoing. After the collection of ECG signals, the research staff manually verified the signals and corrected abnormal R waves. For the baseline period, data were reviewed in two 300-second segments (i.e., baseline 1 and 2) of R-R waves were created.

HR (beats per minute, bpm) was calculated by averaging all valid R-R intervals in each 300-second segment. Additionally, rMSSD (ln[ms^2]) was derived by root mean squaring the successive differences of R-R intervals across time. For the frequency-domain HRV indices, all the 300-second R-R interval segments were filtered using a Hamming window and processed by Fourier transformations with the integration of spectral power in the low (0.04 – 0.15 Hz for LF-HRV) and high (0.15 – 0.50 Hz for HF-HRV) frequency bands to create LF-HRV (ln[ms^2]) and HF-HRV (ln[ms^2]) values. In our study, we focused on baseline cardiac vagal activity collected in the first five minutes (i.e., baseline 1) as five minutes is the standard of conventional short-term recording of HRV (Shaffer & Ginsberg, 2017). Nevertheless, we repeated our analyses using cardiac vagal activity collected in the last five minutes of the baseline period (i.e., baseline 2) to test the robustness of our findings

Table 1
Demographic and physiological characteristics of participants.

	All study participants N = 967	White participants n = 785	Black participants n = 182	Statistical Analysis			
				t / χ^2	p-value	r	95 % CI
Age (years)	54.72 ± 11.78	55.63 ± 11.86	50.74 ± 10.57	4.20	< .001	.17	.12 –.23
Sex	552 (57 %)	432 (55 %)	120 (66 %)	10.25	.001	.10	.04 –.16
Female	415 (43 %)	353 (45 %)	62 (34 %)				
Male							
Currently smoking?	145 (15 %)	86 (11 %)	56 (31 %)	54.71	< .001	.24	.18 –.30
Yes	819 (85 %)	699 (89 %)	126 (69 %)				
No							
Have Regular Physical Activity?	559 (58 %)	424 (54 %)	136 (75 %)	32.84	< .001	.18	.12 – 0.24
Yes	405 (42 %)	361 (46 %)	46 (25 %)				
No							
BMI (kg/m^2)	29.74 ± 6.62	29.04 ± 5.85	32.83 ± 8.60	−7.32	< .001	.29	.23 –.35
Income	58946.62 ± 49807.26	75654.04 ± 59765.40	40239.23 ± 37652.12	8.70	< .001	.33	.23 –.42
Education Level				30.6	< .001	.18	.14 –.28
≤ High School	270 (28 %)	188 (24 %)	82 (45 %)				
Some College	284 (29 %)	220 (28 %)	64 (35 %)				
At least Bachelor's	413 (43 %)	377 (48 %)	36 (20 %)				
Baseline HRV							
$LF_{B1,}$ ln(ms^2)	5.38 ± 1.18	5.37 ± 1.17	5.39 ± 1.23	−.50	.62	.02	−.04 –.08
$HF_{B1,}$ ln(ms^2)	4.86 ± 1.31	4.74 ± 1.26	5.38 ± 1.38	−6.94	< .001	.27	.21 –.33
$rMSSD_{B1,}$ ln(ms^2)	2.91 ± 0.64	2.85 ± 0.62	3.14 ± 0.67	−6.52	< .001	.26	.20 –.32
$HR_{B1,}$ bpm	72.90 ± 10.83	72.72 ± 10.80	73.68 ± 10.93	−1.04	.30	.04	−.02 –.10
Urinary Catecholamines							
Epinephrine adjusted for creatine, ug/g	1.95 ± 1.27	2.04 ± 1.29	1.59 ± 1.12	6.58	< .001	.26	.20 –.32
Norepinephrine adjusted for creatine, ug/g	27.32 ± 14.00	27.88 ± 14.21	24.88 ± 12.79	3.76	< .001	.15	.09 –.21

Note: Data presented as mean ± SD or n (%).
[a]Continuous data was compared using independent t-test and categorical data were compared using χ^2-test
[b]Black participants were primarily recruited from Milwaukee, Wisconsin.
B1 = baseline 1; HRV = heart rate variability; HF = high frequency; HR = heart rate; LF = low frequency; NS = no significant difference (P ≥ 0.05); rMSSD = root mean square of successive differences

(see Supplementary Tables 1–2).

2.2.2. Urinary catecholamine

We assessed urinary catecholamine via epinephrine and norepinephrine. We assessed both catecholamines using unadjusted levels (ug/dL), when adjusting for creatine (ug/g), and when adjusting for total urine volume across the 12-hour sample period (i.e., 12-hour catecholamines, ug/12 hr). In this study, we focused on urinary epinephrine and norepinephrine adjusted for creatine to correct the effects of hydration status in overnight urine production. Dehydrated individuals produce less urine volume with higher hormone concentration compared to hydrated individuals, therefore adjusting for creatine can help to standardize urinary catecholamine concentration (Greenberg and Levine, 1989; Masi et al., 2004). Nevertheless, we repeated our analyses using other indices of urinary catecholamines (i.e., epinephrine, norepinephrine, 12 h epinephrine, and 12 h norepinephrine) to verify our findings (see Supplementary Tables 1–2).

Details of catecholamine collection and assay are outlined in Ryff et al. (2022) and are also available on the MIDUS website (https://midus.wisc.edu/midus2/project4/). Briefly, participants were instructed to provide all urine samples within a 12-hour time frame (7 pm to 7 am) during their visits to the clinical research center. The urine samples treated with 25 mL of 50 % acetic acid and kept in −60°c to −80°c freezers were shipped to the MIDUS Biocore Lab (the University of Wisconsin, Madison, WI). All catecholamine assays were completed at the Mayo Medical Laboratory (Rochester, MN), using High-Pressure Liquid Chromatography procedures (Jiang, 1987; Moyer et al., 1979). 12-hour urinary epinephrine and norepinephrine were calculated as urine volume collected throughout the 12 h multiplied by epinephrine or norepinephrine values and divided by 100 (i.e., [urine volume throughout 12 h * catecholamine]/100). After the assay, urinary epinephrine and norepinephrine values were adjusted for creatine by dividing the epinephrine and norepinephrine values by urine creatine values.

2.2.3. Covariates.

We examined demographic, health, and lifestyle variables associated with changes in cardiac vagal activity and urinary catecholamine as covariates, such as age, sex, household income, education level, BMI, current smoking, and regular physical activity (Bergey et al., 2011; Quintana et al., 2016). Participants self-reported their age, sex (coded as male=1, female=2), mean annual household income, education level (coded as less than or equal to high school=1, some college=2, at least Bachelor's = 3), height (in meters), weight (in kilograms), current smoking (smokes regularly = 1, no or unapplicable = 0), and physical activity. Body mass index (BMI; kg/m^2) was calculated by dividing the participant's weight by the square of height. Participants self-reported whether they did or did not regularly engage in physical activity that lasted at least 20 min at a time, at least 3 times a week, either at work, at home/garden, in sports, or for exercise (Yes=1, No or Unapplicable = 0).

2.3. Data analysis

Analyses were conducted using SPSS (v28.0, IBM Corp). We assessed normality for key study variables. Epinephrine and norepinephrine adjusted for creatine, were log-transformed to correct for substantial skewness. Additionally, we standardized all key variables before analyses. Standardizing key variables after log transformation ensures that all variables contribute equally to all analyses, particularly when dealing with skewed variables or variables on different scales (Warne, 2020). To compare the demographic, cardiac vagal activity, and catecholamine data between White and Black participants, we conducted independent sample t-tests and χ^2-tests. Analysis of covariance (ANCOVA) was used to evaluate mean differences between White and Black participants' baseline cardiac vagal activity and urinary catecholamines variables controlling for covariates. Additionally, to evaluate mean differences across race and sex, we conducted sex-stratified ANCOVA to examine sex differences in baseline cardiac vagal activity and urinary catecholamines variables among both races controlling for covariates. To address our second aim of exploring race and sex differences in the associations of PNS with SNS activity, we examined the partial correlations between baseline cardiac vagal activity and urinary catecholamines among White and Black participants and White and Black female and male participants, controlling for covariates. We evaluated whether the partial correlations across groups were statistically significantly different by conducting the Fisher's *z* test.

3. Results

Table 1 outlines descriptive and physiological characteristics for the full sample and stratified by race. Black participants were on average 5 years younger and had higher BMI than White participants. Compared to White participants, significantly more Black participants endorsed current smoking habits and regular physical activity. Black participants had lower levels of education and had annual incomes that were on average $35,415 less than White participants. Black participants were primarily recruited from the Milwaukee, Wisconsin site.

3.1. Racial and sex differences in cardiac vagal activity and catecholamines

When examining differences in physiological characteristics in our sample, Black participants displayed significantly higher rMSSD and HF-HRV, and significantly lower epinephrine and norepinephrine adjusted for creatine compared to White participants (see *Table 2a*). No racial differences were observed for HR and LF-HRV. Sex-stratified analysis suggested that racial differences in vagal activity and urinary catecholamines emerged almost exclusively among females. We found significantly higher levels of rMSSD and HF-HRV, and lower epinephrine and norepinephrine among Black females compared to White females. White and Black male participants did not reveal significant differences in these physiological markers although the effects were in the same direction as the females (see *Table 2b*).

3.2. Racial and sex differences in correlations between cardiac vagal activity and catecholamines

Results of partial correlations between baseline cardiac vagal activity and urinary catecholamines among White and Black participants are presented in *Table 3a*. Overall, correlations between urinary catecholamines and different indices of cardiac vagal activity were small for both White and Black participants (partial *r*s ranging from −.15 to.24). Among White individuals, we found significant correlations between (1) LF-HRV and norepinephrine adjusted for creatine (partial r = -.11, p = .002), (2) rMSSD and norepinephrine adjusted for creatine (partial r = -.08, p = .03), and (3) HR and norepinephrine adjusted for creatine (partial r = .13, p = .0002).

Among Black participants, we found significant associations between (1) LF-HRV and norepinephrine (partial r = -.15, p = .04), (2) HF-HRV and norepinephrine (partial r = -.15, p = .03), and (3) HR and epinephrine adjusted for creatine (partial r = .16, p = .03), and (4) HR and norepinephrine (partial r = .22, p = .02). We did not find any significant differences in the correlations between urinary catecholamines and cardiac vagal activity variables among White versus Black participants.

Results of partial correlations between baseline cardiac vagal activity and urinary catecholamines among White and Black participants stratified by sex are presented in Table 3b. Among White males, a significant association between HR and norepinephrine (partial r = .11, p = .02) emerged. Among Black males, we found significant associations between (1) HR and epinephrine adjusted for creatine (partial r = .26,

Table 2a.
Physiological characteristics of participants controlling for age, income, education level, sex, BMI, smoking, and physical activity habits stratified by race.

	White participants n = 785	Black participants n = 182	Statistical Analysis			
			F	p-value	r	95 % CI
Baseline Cardiac Vagal Activity						
$LF_{B1,}$ ln(ms^2)	.14 ±.03	−.06 ±.07	.98	.32	.06	−.003 –.12
$HF_{B1,}$ ln(ms^2)	−.07 ±.03	.31 ±.07	22.62	< .001	.14	.08 –.20
$rMSSD_{B1,}$ ln(ms)	−.07 ±.03	.30 ±.07	20.42	< .001	.14	.08 –.20
$HR_{B1,}$ bpm	−.01 ±.03	.05 ±.07	.54	.46	.03	−.03 –.09
Urinary Catecholamines						
Epinephrine adjusted for creatine, ug/g	.06 ±.03	−.25 ±.07	15.97	< .001	.10	.04 –.16
Norepinephrine adjusted for creatine, ug/g	.05 ±.03	−.23 ±.07	13.23	< .001	.10	.04 –.16

Table 2b
Physiological characteristics of participants controlling for age, income, education level, BMI, smoking, and physical activity habits stratified by race and sex.

	White male participants n = 353	Black male participants n = 62	Statistical Analysis			
			F	p-value	r	95 % CI
Baseline Cardiac Vagal Activity						
$LF_{B1,}$ ln(ms^2)	.15 ±.05	−.05 ±.11	2.36	.13	.07	−.03 –.17
$HF_{B1,}$ ln(ms^2)	−.10 ±.05	.11 ±.12	2.53	.11	.07	−.03 –.17
$rMSSD_{B1,}$ ln(ms)	−.04 ±.05	.13 ±.12	1.55	.21	.05	−.05 –.15
$HR_{B1,}$ bpm	−.22 ±.05	−.002 ±.12	2.53	.11	.07	−.03 –.17
Urinary Catecholamines						
Epinephrine adjusted for creatine, ug/g	−.001 ±.05	−.16 ±.12	1.46	.23	.05	−.05 –.15
Norepinephrine adjusted for creatine, ug/g	−.23 ±.04	−.37 ±.11	1.30	.26	.05	−.05 –.15
	White female participants n = 432	**Black female participants** n = 120	F	p-value	r	95 % CI
Baseline Cardiac Vagal Activity						
$LF_{B1,}$ ln(ms^2)	−.09 ±.04	−.09 ±.09	.01	.99	.01	−.07 –.09
$HF_{B1,}$ ln(ms^2)	−.05 ±.04	.40 ±.08	19.58	< .001	.18	.10 –.26
$rMSSD_{B1,}$ ln(ms)	−.09 ±.05	.38 ±.09	20.86	< .001	.18	.10 –.26
$HR_{B1,}$ bpm	.15 ±.04	.10 ±.09	.59	.11	.03	−.05 –.11
Urinary Catecholamines						
Epinephrine adjusted for creatine, ug/g	.11 ±.04	−.32 ±.9	19.49	< .001	.17	.09 –.25
Norepinephrine adjusted for creatine, ug/g	.29 ±.04	−.16 ±.8	22.40	< .001	.18	.10 –.26

Note: Data presented as estimated marginal mean ± standard error.
B1 = baseline 1; B2 = baseline 2; HRV = heart rate variability; HF = high frequency; HR = heart rate; LF = low frequency; rMSSD = root mean square of successive differences

Table 3a.
Correlation between baseline cardiac vagal activity and urinary catecholamines among White and Black participants controlling for participant's age, sex, income, education level, BMI, current smoking, and regular physical activity.

Race	Catecholamines	LF-HRV	HF-HRV	rMSDD	HR
White	Epinephrine adjusted for creatine	−0.01	−0.01	−0.01	0.03
Black	Epinephrine adjusted for creatine	−0.10	−0.08	−0.10	0.16*
White	Norepinephrine adjusted for creatine	−0.11**	−0.07	−0.08*	0.13**
Black	Norepinephrine adjusted for creatine	−0.15*	−0.15*	−0.13	0.22**

$p = .01$), (2) LF-HRV and norepinephrine (partial $r = -.32$, $p = .004$), (3) HF-HRV and norepinephrine (partial $r = -.29$, $p = .03$), rMSDD and norepinephrine (partial $r = -.25$, $p = .03$), and HR and norepinephrine adjusted for creatine (partial $r = .32$, $p = .02$). No correlations between cardiac vagal activity and urinary catecholamines were observed within White and Black females.

Sex-stratified analysis indicated that male participants, but not female participants, displayed racial differences in the association between urinary catecholamines and cardiac vagal activity (see *Table 3b*). In particular, White and Black male participants displayed significantly different correlations between (1) HR and epinephrine adjusted for creatine (White male partial $r = .03$, Black male partial $r = .26$, $z = -1.68$, $p = .03$), (2) LF-HRV and norepinephrine adjusted for creatine (White male partial $r = -0.05$, Black male partial $r = -.32$, $z = 2.00$; 1.89, $p = .03$), and (3) HF-HRV and norepinephrine adjusted for creatine (White male partial $r = -.03$, Black male partial $r = -.29$, $z = 1.91$, $p = .02$).

4. Discussion

This study replicated and extended findings on racial and sex differences in PNS and SNS functioning. It is the first to investigate how race and sex influence the associations between indices of cardiac vagal activity and urinary catecholamines among Black and White participants. Results showed that Black females showing higher HRV and lower catecholamines compared to White females. Small associations between cardiac vagal activity and catecholamines were identified, varying by race, sex, and ANS index, with more robust effects in males than females. Nevertheless, these findings should be interpreted with caution as Black participants were primarily recruited from Milwaukee, Wisconsin, which limits generalizability to Black individuals across other geographic contexts.

4.1. Racial and sex differences in cardiac vagal activity and catecholamines

Consistent with previous findings (Hill and Thayer, 2019), Black participants displayed more cardiac activity (i.e., rMSSD and HF-HRV) at rest, indicating higher PNS activity, than White participants. We found no racial differences in HR, aligning with a longitudinal study suggesting attenuated racial differences in HR among middle-aged

Table 3b.
Correlation between baseline cardiac vagal activity and urinary catecholamines among White and Black female and male participants controlling for participant's age, income, education level, BMI, current smoking, and regular physical activity.

Race/ sex	Catecholamines	LF-HRV	HF-HRV	rMSDD	HR
White male	Epinephrine adjusted for creatine	0.06	0.10	0.02	0.03[x]
Black male	Epinephrine adjusted for creatine	−0.11	−0.09	−0.11	0.26*[x]
White female	Epinephrine adjusted for creatine	−0.05	−0.02	−0.01	0.02
Black female	Epinephrine adjusted for creatine	−0.06	−0.08	−0.08	0.09
White male	Norepinephrine adjusted for creatine	−0.05[x]	−0.03[x]	−0.03	0.11*
Black male	Norepinephrine adjusted for creatine	−0.32**[x]	−0.29*[x]	−0.25*	0.32*
White female	Norepinephrine adjusted for creatine	−0.05	−0.06	−0.04	0.06
Black female	Norepinephrine adjusted for creatine	−0.07	−0.13	−0.11	0.16

Note: *p < 0.05, ** p < 0.01; [x] Significant racial differences in correlation (p < 0.05); HRV = heart rate variability; HF = high frequency; HR = heart rate; LF = low frequency; rMSSD = root mean square of successive differences.
[x] Significant racial differences in correlation (p < 0.05):

- HR and epinephrine adjusted for creatine (White male partial r = .03, Black male partial r = .26, z = -1.68, p = .03)
- LF-HRV and norepinephrine adjusted for creatine (White male partial r = -0.05, Black male partial r = -.32, z = 2.00; 1.89, p = .03),
- HF-HRV and norepinephrine adjusted for creatine (White male partial r = -.03, Black male partial r = -.29, z = 1.91, p = .02).

adults (Colangelo et al., 2020). Similar to previous studies (Shekh, 2016; Wang et al., 2005), no racial differences in LF-HRV were observed. However, contrary to most studies that revealed no racial differences in catecholamines (Blaudeau et al., 2008; Homandberg and Fuller-Rowell, 2020; Masi et al., 2004; van Berge-Landry et al., 2008; Walker et al., 1992), we found that Black participants exhibited significantly lower epinephrine and norepinephrine adjusted for creatine after controlling for covariates, with small effect size. This difference may stem from our larger sample size, which permitted control of covariates and increased power to detect smaller effects. Notably, many previous studies had small sample sizes or did not account for key covariates like age.

We found that Black participants had lower catecholamine levels (i.e., epinephrine and norepinephrine adjusted for creatine) than White participants, suggesting lower SNS activity. Previous research showed mixed findings on SNS activity in Black participants, who have shown higher TPR (higher SNS activity; Brownlow et al., 2020) but lower electrodermal activity (EDA, which implies lower SNS activity; Chong et al., 2023) than White participants. Literature on other SNS indices, such as pre-ejection period and salivary alpha-amylase, is sparse, but suggests no racial differences in resting PEP activity and the need for further investigation of racial differences in salivary alpha-amylase (Brownlow et al., 2020; Chong et al., 2023). Our findings highlight that labeling different SNS indices as "general SNS activity" obscures the complexity of autonomic influences. For instance, despite having similar chemical characteristics, epinephrine and norepinephrine exert different influences on the adrenergic receptors (receptors that target catecholamines). Specifically, α-adrenergic receptors sympathetically mediate vasoconstrictive responses and are mainly found in the arteries, whereas β-adrenergic receptors sympathetically mediate vasodilation responses and are present in smooth muscles of the lungs, heart, and arteries. Epinephrine has a greater effect on beta-adrenergic receptors compared to norepinephrine (Goldstein, 2003), while TPR primarily reflects α-adrenergic activity (Lyssand et al., 2008). Furthermore, EDA primarily reflects cholinergic rather than adrenergic SNS activity (Turpin and Grandfield, 2009). Future studies should specify which aspect of SNS functioning is measured and consider the physiological implications of each index.

Sex significantly influenced cardiac activity and catecholamine levels. Black and White females, but not males, displayed significantly higher levels of cardiac activity (i.e., rMSSD, HF-HRV, and HR) and lower catecholamine levels (i.e., epinephrine and norepinephrine adjusted for creatine). Given that our sample included more Black females (n = 120, 22 % of all females) than Black males (n = 62, 15 % of all males), this imbalance may have contributed to the observed racial differences being more pronounced among females. Future studies with larger and more balanced samples of Black males and females are needed to replicate these findings.

The observation of elevated cardiac activity in women is consistent with prior literature reporting higher HRV and HR in females than males (Koenig and Thayer, 2016). Similarly, recent work has shown that at a given HR, females exhibit higher HRV than males (Williams et al., 2022). Several psychosocial and biological mechanisms may explain these sex differences. Social factors such as increased stress exposure and sociocultural expectations for emotion regulation and expression may lead women to engage in more parasympathetic-dominant strategies (e.g., tend-and-befriend), which promote vagal activation, while men may rely more on fight-or-flight responses involving vagal withdrawal (Calderón-García et al., 2024; Spangler et al., 2021; Taylor and Master, 2011). This divergence may help explain higher cardiac activity in women compared to men.

Biologically, hormonal and receptor-based factors may also play a role. Estrogen, which is higher in females, has been linked to autonomic regulation and cardioprotection. Specifically, estrogen may contribute to higher HRV and lower catecholamines by enhancing acetylcholine sensitivity and dampening SNS activity (Dart et al., 2002; Ndzie Noah et al., 2021). Increased acetylcholine sensitivity in women may reduce catecholamine release, supporting the pattern of elevated parasympathetic and reduced sympathetic activity. Furthermore, sex differences in adrenergic receptor function, such as higher alpha-adrenergic receptor density in females, may also contribute to reduced SNS output and stronger PNS responses (Dart et al., 2002; Regitz-Zagrosek et al., 2013). Thus, rather than being driven by a single mechanism, these sex differences in autonomic activity are likely shaped by an interplay of hormonal, neurochemical, and sociocultural factors.

Our finding that females exhibited lower catecholamine levels, paired with higher HRV and HR align with prior research and theoretical frameworks (e.g., Williams et al., 2022) and contribute to the scarce and mixed literature evaluating sex differences in catecholamine levels (Hansen et al., 2001; James, 2018; Masi et al., 2004; Reuben et al., 2000). Our results align with those of Hansen et al. (2001) who found lower catecholamines adjusted for creatine among women compared to men, but contrasts with findings by James (2018) that Black women had higher levels of catecholamines compared to women of other races and ethnicities. Moreover, while Masi et al. (2004) and Reuben et al. (2000) both reported higher creatine-corrected epinephrine in women compared to men, Masi et al. (2004) found higher catecholamines in Black participants compared to White participants whereas Rueben et al. (2000) revealed no racial differences in catecholamines. Although Black and White males in our study did not display statistically significant differences in mean HRV and catecholamines, the direction and effect sizes of mean differences between racial groups were similar to those observed among females, suggesting that sex-specific patterns may generalize.

4.2. Racial and sex differences in correlations between cardiac vagal activity and catecholamines

Overall, race and sex differences in catecholamine-cardiac activity only emerged between Black and White men, such that they were significantly inversely correlated for Black men only. In Black and White

men, we observed small positive associations between HR and catecholamines and small inverse relations between HRV indices and catecholamines. Greater epinephrine and norepinephrine correlated with greater HR, which aligns with understanding that SNS-induced catecholamine release serves to accelerate HR (Hall, 2015). Moreover, higher levels of LF-HRV and HF-HRV were associated with lower levels of catecholamine, replicating and extending prior evidence of a small inverse relation between HF-HRV and urinary epinephrine and norepinephrine (Lee et al., 2010 using HF-HRV; Thayer and Fischer, 2013 using RMSSD).

Our findings provide additional nuance to the understanding of the "cardiovascular conundrum" phenomenon. Specifically, our results that Black participants exhibited lower SNS activity, indexed via urinary catecholamines, underscores that greater TPR among Black Americans likely is not solely attributed to generalized SNS activation. Instead, SNS activation among Black participants might be more localized within the vascular system and differentially associated with alpha- and beta-adrenergic activity, aligning with previous works (Anderson; 1989; Taherzadeh et al., 2010). On the other hand, our preliminary findings of lower catecholamines in Black participants suggest a reduction in beta-adrenergic activity. This distinction aligns with prior research showing mixed evidence for lower SNS among Black Americans when using indices such as electrodermal activity (Chong et al., 2023). To better understand these complex autonomic dynamics, future research should clearly delineate between the distinct roles of alpha versus beta adrenergic activity in the SNS, moving beyond broad generalizations about SNS activity. Studies using underutilized SNS indices (e.g., salivary alpha-amylase) could help clarify mechanisms of autonomic dysregulation across racial groups and its implications for cardiovascular health.

Nevertheless, the associations between urinary catecholamines and cardiac vagal activity varied by race and ANS indices. While a few significant correlations emerged between different indices of cardiac vagal activity (i.e., LF-HRV, HF-HRV, HR) and norepinephrine adjusted for creatine in both Black and White participants, most correlations were not significant. These differences may be informed by underlying neurophysiological mechanisms. Specifically, short latency sympathetic pre-ganglionic neurons, linked to adrenal norepinephrine, are influenced by the vagally mediated baroreflex activity, whereas long latency neurons, associated with adrenal epinephrine, are less affected (Morrison, 2001). Therefore, the observed differential associations between vagally mediated HRV and catecholamines are not unexpected.

Sex-specific differences were also evident. Racial differences in the associations between HRV and catecholamine levels were most pronounced between Black and White males. This result aligned with some studies that reported small inverse correlations between HRV and catecholamines (Lee et al., 2010 using HF-HRV; Thayer and Fischer, 2013 using RMSSD), but in contrast to other studies (e.g., Fagundes et al., 2011; Sloan et al., 1996; Vlcek et al., 2008) that revealed null correlations. Notably, the non-significant correlations were based on males and females (Sloan et al., 1996; Vlcek et al., 2008) or females only samples (Fagundes et al., 2011).

Importantly, HR was more strongly correlated with epinephrine/norepinephrine adjusted for creatine in Black males than in White males, despite both groups exhibiting similar overall catecholamine levels. Our findings align with Walker et al. (1992), who observed that Black adults exhibited increased TPR with lower plasma norepinephrine during exercise, in contrast to White adults who showed increases in both. This pattern may point to altered sympathoadrenal function, such as differences in adrenergic receptor sensitivity, in Black adults. Prior work has shown that Black individuals may have blunted β-adrenergic and heightened α-adrenergic receptor responsiveness (Mills et al., 1995; Sherwood et al., 2017). Such receptor dynamics could contribute to increased HR, decreased cardiac output, and increased TPR, which are characteristics of hypertensive patients (Mills et al., 1995; Sherwood et al., 2017). Thus, future studies should investigate how catecholamines, adrenergic receptor sensitivity, TPR, and HR interact, particularly as potential mechanisms for racial disparities in autonomic functioning.

In addition to neurophysiological factors, variation in body composition may also help explain racial and sex differences in HRV-catecholamine links (James, 2018; Li et al., 2009; Masi et al., 2004). Since both PNS and SNS regulate energy consumption and fat metabolism, BMI may influence ANS functioning (Guarino et al., 2017; Masi et al., 2004). We ran exploratory moderation analyses to determine if BMI influences the relationship between HRV and catecholamines. BMI did not moderate the association between HRV indices (HR, LF-HRV, HF-HRV, RMSSD) and catecholamines (i.e., epinephrine and norepinephrine adjusted for creatine). However, because we lacked muscle mass data, we could not replicate Masi et al. (2004)'s finding that muscle mass (not BMI) was positively correlated with creatine-adjusted catecholamine levels. Despite this limitation, we found that higher BMI significantly influenced the relationship between HR and norepinephrine12 hours, $R^2 = .08$, $F(3, 964) = 28.55$, $p = .001$, $\Delta R^2 = .004$, and between HF-HRV and norepinephrine 12 h, $R^2 = .08$, $F(3, 964) = 30.95$, $p = .001$, $\Delta R^2 = .004$. These findings suggest that BMI may influence the coupling between vagal and sympathetic indices. Concordantly, Chang et al. (2021) found that nurses with overly high BMI (i.e., overweight/obese) displayed significantly lower HRV indices (i.e., LF-HRV, very low-frequency HRV, and standard deviation of normal-to-normal interval HRV) compared to nurses with lower BMI scores, controlling for age and shift type. This finding further illustrates how body composition may affect ANS functioning and highlights the need for future studies to explore additional moderators of race and sex effects on ANS activity.

4.3. Cardiac vagal activity-catecholamines links and health

The observed race and sex differences in vagal-catecholamine associations carry important implications for understanding cardiovascular health disparities. Compared to White individuals, Black individuals may demonstrate greater alpha-adrenergic activity (high TPR) and reduced beta-adrenergic activity (low catecholamine). These biological differences in ANS regulation may interact in complex ways to influence health outcomes. Specifically, dysregulated PNS-SNS interactions have been linked to emotional and physiological conditions, including distress and anxiety, which are implicated in cardiovascular risk (Chong et al., 2022; Thayer et al., 2020; Bajkó et al., 2012). For example, stronger HRV-catecholamine correlations in Black men may reflect adrenergic dysregulation that contributes to cardiovascular vulnerability (Mills et al., 1995; Sherwood et al., 2017). In contrast, higher HRV in Black women may confer some protective effects due to enhanced emotion regulation capacity (Thayer et al., 2020). These patterns lend support to the cardiovascular conundrum theory (Hill and Thayer, 2019), which posits that paradoxical SNS and PNS activity may result in maladaptive cardiovascular responses, particularly in marginalized groups. Understanding these dynamics could inform more precise and culturally sensitive approaches to intervention.

One promising avenue is the use of biofeedback interventions, which have been shown to reduce blood pressure and improve autonomic balance (Jenkins et al., 2024; Vaschillo et al., 2002). Tailoring such interventions to the specific autonomic profiles of different racial and sex groups could enhance their effectiveness. In summary, future research should continue exploring the intersection of ANS function, race, and sex to refine predictive models and intervention strategies. A more nuanced, systems-level understanding of autonomic regulation will be key to addressing cardiovascular health disparities (Chong et al., 2023; Lyssand et al., 2008; Williams et al., 2022)."

4.4. Limitations and future directions

This study has several limitations. Our study included a modest sample of Black participants (n = 182) compared to White participants

(n = 785), which may limit the ability to detect weak effect sizes or small racial and sex differences in associations between vagal activity and catecholamines. Moreover, Black participants were recruited only from Milwaukee, Wisconsin, which limits generalizability to Black individuals elsewhere in the United States. Future studies should include larger, nationally representative samples of Black participants, as well as other racial groups. Moreover, Black participants had lower levels of education and household income than White participants, which could affect the physiological differences observed. In addition, our findings based on stratified analyses may not reflect significant interactive effects of race and sex on cardiac activity, catecholamines, and its association; thus, warrants further inquiry that involve more complex analytic approaches.

The underlying factors associated with increased risk of cardiovascular racial disparities are, to date, not fully understood. While some of this is thought to reflect measurement and other error, social and environmental determinants of health that disproportionately impact some subgroups more than others (e.g., Black individuals, women) likely also influence physiological functioning (Chong et al., 2023; Thayer et al., 2020). Since race is a social construct with no distinct biological basis, future research should incorporate social and environmental determinants of health, as prior studies suggest that perceived discrimination, chronic stress, socioeconomic status, and neighborhood environment may contribute to physiological differences (Hill and Thayer, 2019; Kemp et al., 2016; Rosati et al., 2021). For example, Harnett et al. (2019) found that racial differences in SNS activity (i.e., EDA) between White and Black participants were attenuated after adjusting for income, neighborhood disadvantages, and violence exposure. Moreover, Tomfohr et al. (2016) found that race influences physiological (dys)regulation through discrimination exposure, negative affect (e.g., anger), and health practices (e.g., sleep). Similar patterns have also emerged in studies of other minoritized populations, such that sexual minority individuals have been found to exhibit higher SNS activity (i.e., TPR), compared to heterosexual individuals (Rosati et al., 2021), indicating that frequent discrimination and stress exposure secondary to marginalization may play significant role in increasing the risk for cardiovascular health problems. Thus, further research to understand the role that psychosocial factors may play in ANS regulation and its implications for racial health disparities.

Despite limitations, our findings offer a more nuanced understanding of how these factors intersect to shape cardiovascular health risk. Our results indicate that Black females exhibit elevated cardiac vagal activity and lower sympathetic activity, which may offer some protective physiological effects. On the other hand, Black males show stronger associations between sympathetic markers and cardiovascular responses, which may reflect increased vulnerability. These findings underscore the importance of disaggregating physiological data by race and sex and using multiple ANS indices to avoid misleading generalizations. Future studies should consider the implications of demographic variables as the main effects or covariates. Further, researchers should consider including sensitivity analyses and running subgroup analyses to support interpretations in order to establish the functional equivalence of physiological measures across groups (Chong et al., 2023). Ultimately, this research lays the groundwork for culturally tailored interventions, such as biofeedback or stress-reduction programs, designed to address distinct autonomic profiles and reduce cardiovascular health disparities.

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Data statement

Data are available through the Midlife in the United States (MIDUS) website (https://midus.wisc.edu/midus2/project4/).

CRediT authorship contribution statement

Betty Lin: Writing – review & editing. **Li Shen Chong:** Writing – review & editing, Writing – original draft, Visualization, Formal analysis, Data curation, Conceptualization. **Williams Dewayne P.:** Writing – review & editing. **Elana B. Gordis:** Writing – review & editing. **Julian F. Thayer:** Writing – review & editing, Supervision.

Declaration of Competing Interest

No conflicts of interest.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.psyneuen.2025.107527.

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