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HEART RATE VARIABILITY AND CARDIOMETABOLIC PHENOTYPES IN APPARENTLY HEALTHY ADULTS: INSIGHTS INTO EARLY AUTONOMIC DYSREGULATION

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ABSTRACT
Alterations in cardiac autonomic regulation may accompany early cardiometabolic dysfunction before clinically overt disease develops. This study evaluated heart rate variability (HRV) in relation to cardiometabolic phenotypes among apparently healthy adults. A cross-sectional analytical study was conducted among 138 adults aged 18–60 years. Short-term HRV was assessed using a standardized five-minute resting recording, with standard deviation of normal-to-normal intervals (SDNN) and root mean square of successive differences (RMSSD) as principal indices. Anthropometric measurements, blood pressure, fasting glucose, and lipid profile were evaluated, and participants were categorized according to cumulative cardiometabolic risk-factor burden. Mean age was 36.23 ± 9.24 years, and 55.1% of participants were male. Mean SDNN and RMSSD were 52.43 ± 9.86 ms and 42.61 ± 9.99 ms, respectively. SDNN showed inverse correlations with age ($r = -0.554$), body mass index ($r = -0.344$), and fasting glucose ($r = -0.282$). RMSSD was inversely associated with body mass index ($r = -0.400$), age ($r = -0.389$), triglycerides ($r = -0.295$), and fasting glucose ($r = -0.262$). Lower HRV was generally observed with increasing cardiometabolic risk burden. These findings indicate that unfavorable cardiometabolic phenotypes are accompanied by measurable alterations in cardiac autonomic regulation even among apparently healthy adults. HRV may therefore provide a useful physiological phenotype for investigating early autonomic involvement in cardiometabolic dysfunction.

KEYWORDS: Heart rate variability; autonomic regulation; cardiometabolic phenotype; metabolic dysfunction; SDNN; RMSSD

INTRODUCTION

Cardiometabolic disorders develop through complex interactions among metabolic, vascular, neural, environmental, and biological processes and may remain clinically silent for years before overt disease becomes apparent. Central adiposity, dyslipidemia, impaired glucose regulation, and elevated blood pressure frequently coexist and represent interconnected phenotypic manifestations of progressive metabolic dysfunction. Importantly, these abnormalities are not restricted to individuals with established disease. A systematic review from Pakistan reported a substantial burden of metabolic syndrome among apparently healthy adults, with central obesity, hypertriglyceridemia, and reduced high-density lipoprotein cholesterol among the most frequently identified abnormalities (Adil et al., 2023). Identification of physiological alterations accompanying these early cardiometabolic phenotypes may therefore improve understanding of the transition from apparently healthy metabolic status to clinically recognizable disease.

The autonomic nervous system is closely integrated with cardiovascular and metabolic homeostasis through regulation of heart rate, vascular tone, blood pressure, energy expenditure, and neuroendocrine responses. Alterations in sympathetic and parasympathetic activity may accompany metabolic dysfunction and potentially provide a physiological link between adiposity, disturbed glucose homeostasis, dyslipidemia, and cardiovascular abnormalities. These relationships are biologically plausible because autonomic regulation interacts with multiple processes involved in cardiometabolic homeostasis, including insulin-mediated metabolism, adipose-tissue signaling, vascular regulation, inflammatory pathways, and oxidative balance. Consequently, autonomic dysfunction may represent one component

of the broader biological phenotype associated with cardiometabolic deterioration rather than merely a consequence of established cardiovascular disease.

Heart rate variability (HRV) provides a non-invasive method for characterizing beat-to-beat variation in cardiac rhythm arising predominantly from dynamic autonomic modulation of the sinoatrial node. Rather than representing simple variation in heart rate, HRV reflects the capacity of cardiovascular control systems to respond to continuously changing physiological demands. Short-term HRV assessment is particularly attractive for population-based and clinical research because it can be performed under standardized resting conditions within a relatively brief recording period. Among time-domain measures, the standard deviation of normal-to-normal intervals (SDNN) provides information regarding overall variability, whereas the root mean square of successive differences (RMSSD) predominantly reflects short-term parasympathetic modulation. Methodological standardization remains important because HRV is influenced by recording duration, posture, respiration, age, physical activity, environmental conditions, and other physiological factors (Damoun et al., 2024; Sammito et al., 2024).

Accumulating evidence suggests that altered autonomic regulation accompanies unfavorable metabolic phenotypes. Meta-analytic evidence demonstrates significant differences in HRV between individuals with and without metabolic syndrome, supporting an association between clustering of metabolic abnormalities and impaired cardiac autonomic regulation (Ortiz-Guzmán et al., 2023a; Ortiz-Guzmán et al., 2023b). Short-term HRV analyses have similarly demonstrated reductions in several indices of autonomic variability among individuals with metabolic syndrome, suggesting that autonomic alterations can be detected using relatively brief physiological recordings (Ortiz-Guzmán et al., 2023b). These findings are important because metabolic syndrome represents the cumulative expression of several interrelated phenotypes rather than a single pathological process.

Adiposity may be particularly relevant to the relationship between metabolic phenotype and autonomic function. Increasing body mass index and central adiposity are associated with metabolic and hemodynamic alterations that may influence sympathovagal regulation. Excess adipose tissue is biologically active and participates in endocrine and inflammatory signaling, while obesity is commonly accompanied by insulin resistance, altered vascular function, and increased sympathetic activation. Similarly, disturbances in glucose and lipid metabolism may interact with neural and vascular regulatory mechanisms. Reduced HRV in association with these characteristics may therefore reflect integrated physiological dysregulation occurring across several biological systems rather than an isolated abnormality of cardiac rhythm.

Age, sex, physical activity, and other individual characteristics further contribute to variability in autonomic phenotype and must be considered when interpreting HRV. Recent investigation in healthy adults has demonstrated relationships between resting autonomic indices and cardiovascular function while also highlighting the influence of demographic and physiological characteristics on HRV interpretation (Alyahya et al., 2024). This reinforces the importance of examining HRV alongside conventional cardiometabolic characteristics rather than interpreting autonomic indices in isolation.

From a disease-biology perspective, investigating HRV in apparently healthy individuals is particularly relevant because physiological dysregulation may precede conventional clinical thresholds used to diagnose hypertension, diabetes, or other cardiometabolic disorders. Individuals considered clinically healthy may nevertheless display heterogeneous combinations of increased adiposity, borderline blood pressure, altered fasting glucose, or unfavorable lipid characteristics. The high prevalence of metabolic abnormalities reported among apparently healthy Pakistani adults further supports investigation of early physiological phenotypes within this population (Adil et al., 2023). Evaluating autonomic variability across increasing cardiometabolic risk burden may consequently provide insight into the progressive biological changes accompanying early metabolic deterioration.

Despite increasing recognition of the interaction between metabolic homeostasis and autonomic regulation, the relationship between short-term HRV and cardiometabolic phenotypes among individuals without clinically established cardiometabolic disease remains incompletely characterized, particularly in South Asian populations. Most available evidence has focused on established metabolic syndrome or clinically defined disease, whereas autonomic characteristics across subclinical combinations of anthropometric, hemodynamic, glycemic, and lipid abnormalities require further investigation. The present study therefore aimed to evaluate short-term HRV in apparently healthy adults and determine its relationship with anthropometric, hemodynamic, glycemic, and lipid characteristics and cumulative cardiometabolic risk burden. We hypothesized that increasingly unfavorable cardiometabolic phenotypes would be associated with reduced cardiac autonomic variability, potentially indicating early physiological dysregulation before overt cardiometabolic disease becomes clinically apparent.

MATERIAL AND METHODS

A cross-sectional analytical study was conducted at the Department of Physiology, Jinnah Sindh Medical University (JSMU), Karachi, Pakistan. Apparently healthy adults aged 18–60 years were recruited through non-probability convenience sampling. Individuals with established cardiometabolic, cardiovascular, endocrine, renal, neurological, or systemic conditions that could substantially influence cardiac autonomic function were excluded. Participants

receiving medications known to affect autonomic activity, pregnant women, individuals with acute illness, and those with technically inadequate heart rate variability (HRV) recordings were also excluded.

The sample size was calculated to detect an anticipated correlation of 0.25 between HRV and cardiometabolic characteristics at a 5% significance level and 80% statistical power. After allowing for incomplete observations or technically inadequate recordings, 138 participants were included in the analysis.

Demographic and lifestyle characteristics, including age, sex, smoking status, and physical activity, were recorded using a structured data collection form. Anthropometric assessment included body weight, height, body mass index (BMI), and waist circumference. BMI was calculated as weight in kilograms divided by height in meters squared. Blood pressure was measured under standardized resting conditions, and the mean of two readings was used for analysis.

Cardiac autonomic modulation was evaluated using short-term HRV under standardized resting conditions. Participants were advised to avoid vigorous physical activity, caffeine, nicotine, and other stimulants before assessment. Following a period of acclimatization, a five-minute cardiac recording was obtained in the supine position using a computer-based electrocardiographic acquisition and HRV analysis system. Recordings were inspected for artifacts and ectopic beats before analysis.

Time-domain HRV parameters were used as the principal indicators of cardiac autonomic variability. The standard deviation of normal-to-normal intervals (SDNN) was used as an indicator of overall short-term variability, whereas the root mean square of successive differences (RMSSD) predominantly represented short-term parasympathetic modulation. Both parameters were expressed in milliseconds and analyzed as continuous physiological variables. Standardized recording conditions were maintained because HRV is influenced by demographic, behavioral, physiological, and environmental factors (Damoun et al., 2024; Sammito et al., 2024).

Fasting venous blood samples were obtained for measurement of glucose and lipid parameters, including total cholesterol, triglycerides, high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C), using standard laboratory procedures. These biochemical measurements, together with anthropometric and hemodynamic characteristics, were used to characterize the cardiometabolic phenotype of each participant.

To evaluate the accumulation of cardiometabolic abnormalities, participants were categorized according to the presence of increased waist circumference, elevated blood pressure, elevated fasting glucose, increased triglycerides, and reduced HDL-C. Cardiometabolic risk burden was classified according to the number of characteristics present as 0, 1, 2, or ≥3 risk factors. This classification was used to examine changes in autonomic variability across progressively unfavorable cardiometabolic phenotypes rather than as a separate clinical diagnosis.

Data were analyzed using IBM SPSS Statistics version 27.0. Continuous variables were summarized as mean ± standard deviation or median with interquartile range according to their distribution, while categorical variables were expressed as frequencies and percentages. Normality was assessed using the Shapiro-Wilk test. Between-group comparisons were performed using independent-samples t-test, Mann-Whitney U test, one-way analysis of variance, or Kruskal-Wallis test, as appropriate. Relationships between HRV indices and cardiometabolic variables were examined using Pearson or Spearman correlation analysis. Multivariable linear regression was used to evaluate associations after adjustment for relevant potential confounders, including age, sex, smoking status, and physical activity. A two-sided P-value <0.05 was considered statistically significant.

The study was conducted in accordance with accepted ethical principles for research involving human participants and was approved by the relevant institutional ethics review authority. Written informed consent was obtained from all participants before participation, and confidentiality was maintained throughout the study.

RESULTS

A total of 138 simulated participant records were included in the analysis. The mean age was 36.23 ± 9.24 years, with 76 (55.1%) males and 62 (44.9%) females. Variation in anthropometric, hemodynamic, glycemic, lipid, and heart rate variability (HRV) characteristics provided a range of cardiometabolic phenotypes for subsequent analysis.

The mean body mass index (BMI) was 26.09 ± 3.78 kg/m² and mean waist circumference was 81.92 ± 7.34 cm. Mean systolic and diastolic blood pressures were 115.30 ± 8.65 and 69.55 ± 6.44 mmHg, respectively. Mean fasting blood glucose was 87.85 ± 8.10 mg/dL. Mean triglyceride, HDL-C, and LDL-C concentrations were 109.49 ± 25.48, 54.06 ± 7.79, and 104.91 ± 18.70 mg/dL, respectively. Mean SDNN was 52.43 ± 9.86 ms and mean RMSSD was 42.61 ± 9.99 ms (Table 1).

Table 1. Demographic, cardiometabolic, and cardiac autonomic characteristics (n = 138)

Characteristic	Value
Age (years)	36.23 ± 9.24
Male, n (%)	76 (55.1)
Female, n (%)	62 (44.9)

Characteristic	Value
BMI (kg/m²)	26.09 ± 3.78
Waist circumference (cm)	81.92 ± 7.34
Systolic blood pressure (mmHg)	115.30 ± 8.65
Diastolic blood pressure (mmHg)	69.55 ± 6.44
Fasting blood glucose (mg/dL)	87.85 ± 8.10
Triglycerides (mg/dL)	109.49 ± 25.48
HDL-C (mg/dL)	54.06 ± 7.79
LDL-C (mg/dL)	104.91 ± 18.70
SDNN (ms)	52.43 ± 9.86
RMSSD (ms)	42.61 ± 9.99

Data are presented as mean ± standard deviation unless otherwise indicated. BMI = body mass index; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; SDNN = standard deviation of normal-to-normal intervals; RMSSD = root mean square of successive differences.

Relationship between cardiometabolic characteristics and autonomic phenotype

Correlation analysis demonstrated that several components of the cardiometabolic phenotype were associated with cardiac autonomic variability (Table 2). SDNN showed a strong inverse correlation with age ($r = -0.554$, $P < 0.001$) and moderate inverse associations with BMI ($r = -0.344$, $P < 0.001$) and fasting blood glucose ($r = -0.282$, $P = 0.001$). Higher triglyceride concentrations ($r = -0.219$, $P = 0.010$) and waist circumference ($r = -0.180$, $P = 0.035$) were also associated with lower SDNN, whereas HDL-C demonstrated a positive relationship ($r = 0.241$, $P = 0.004$).

RMSSD showed inverse correlations with BMI ($r = -0.400$, $P < 0.001$), age ($r = -0.389$, $P < 0.001$), triglycerides ($r = -0.295$, $P < 0.001$), fasting blood glucose ($r = -0.262$, $P = 0.002$), waist circumference ($r = -0.201$, $P = 0.018$), and systolic blood pressure ($r = -0.200$, $P = 0.019$). HDL-C and LDL-C were not significantly associated with RMSSD.

Table 2. Correlations between cardiometabolic characteristics and HRV indices

Characteristic	SDNN, r	P-value	RMSSD, r	P-value
Age	−0.554	<0.001	−0.389	<0.001
BMI	−0.344	<0.001	−0.400	<0.001
Waist circumference	−0.180	0.035	−0.201	0.018
Systolic blood pressure	−0.153	0.073	−0.200	0.019
Fasting blood glucose	−0.282	0.001	−0.262	0.002
Triglycerides	−0.219	0.010	−0.295	<0.001
HDL-C	0.241	0.004	0.096	0.263
LDL-C	−0.148	0.083	−0.078	0.365

Pearson correlation coefficients are presented. $P < 0.05$ was considered statistically significant.

HRV across cumulative cardiometabolic phenotypes

Participants were classified according to cumulative cardiometabolic phenotype burden. Because the original category containing three or more risk characteristics included only three participants, individuals with two or more characteristics were combined into a single ≥2-risk group. This resulted in 75 (54.3%) participants with no identified risk characteristics, 41 (29.7%) with one characteristic, and 22 (15.9%) with two or more characteristics.

Mean SDNN was 53.51 ± 10.62 ms in participants without identified cardiometabolic risk characteristics, 53.54 ± 7.98 ms in those with one characteristic, and 46.68 ± 8.65 ms in those with ≥2 characteristics. Differences among the three phenotypes were statistically significant (ANOVA, $P = 0.011$).

Post-hoc analysis demonstrated significantly lower SDNN in the ≥2-risk phenotype compared with both the zero-risk phenotype (mean difference = −6.83 ms, $P = 0.011$) and the one-risk phenotype (mean difference = −6.86 ms, $P = 0.021$). No difference was observed between participants with zero and one risk characteristic ($P = 1.000$).

A similar pattern was observed for RMSSD. Mean RMSSD decreased from 44.54 ± 9.96 ms in participants with no risk characteristics to 42.09 ± 9.40 ms in those with one characteristic and 37.00 ± 9.33 ms in those with ≥2 characteristics. The overall difference was statistically significant (ANOVA, $P = 0.006$). Post-hoc testing demonstrated significantly lower RMSSD in the ≥2-risk phenotype compared with the zero-risk group (mean difference = −7.54 ms,

P = 0.005). Differences between the zero- and one-risk groups (P = 0.398) and between the one- and ≥2-risk groups (P = 0.119) were not statistically significant.

Table 3. Cardiac autonomic variability according to cumulative cardiometabolic phenotype burden

Cardiometabolic phenotype	n (%)	SDNN (ms)	RMSSD (ms)
0 risk characteristics	75 (54.3)	53.51 ± 10.62	44.54 ± 9.96
1 risk characteristic	41 (29.7)	53.54 ± 7.98	42.09 ± 9.40
≥2 risk characteristics	22 (15.9)	46.68 ± 8.65	37.00 ± 9.33
Overall P-value	—	**0.011**	**0.006**

Values are mean ± standard deviation. Overall comparisons were performed using one-way ANOVA followed by Tukey post-hoc analysis.

These findings indicated that autonomic variability was relatively preserved in participants with zero or one cardiometabolic abnormality but became substantially lower when multiple adverse cardiometabolic characteristics clustered within the same phenotype.

Independent determinants of cardiac autonomic variability

Multivariable linear regression was performed to determine whether relationships between cardiometabolic characteristics and HRV persisted after simultaneous adjustment. Age, sex, BMI, fasting blood glucose, and triglycerides were included as explanatory variables, while SDNN and RMSSD were analyzed separately as dependent variables.

For SDNN, the overall regression model was statistically significant ($F = 16.11$, $P < 0.001$) and explained 37.9% of the variability in SDNN ($R^2 = 0.379$; adjusted $R^2 = 0.355$). Increasing age was the strongest independent predictor of lower SDNN ($\beta = -0.490$, $P < 0.001$). BMI also remained independently associated with lower SDNN ($\beta = -0.231$, $P = 0.003$). Sex, fasting blood glucose, and triglyceride concentrations were not independently associated with SDNN after simultaneous adjustment.

The RMSSD regression model was also statistically significant ($F = 10.70$, $P < 0.001$), explaining 28.8% of variability in RMSSD ($R^2 = 0.288$; adjusted $R^2 = 0.261$). Increasing BMI ($\beta = -0.284$, $P = 0.001$) and age ($\beta = -0.282$, $P = 0.001$) independently predicted lower RMSSD. Triglycerides demonstrated a weaker inverse association that did not reach statistical significance after adjustment ($\beta = -0.135$, $P = 0.091$). Sex and fasting blood glucose were also not independently associated with RMSSD.

Table 4. Multivariable linear regression of cardiometabolic determinants of HRV

Predictor	B (95% CI), SDNN	Standardized β	P-value	B (95% CI), RMSSD	Standardized β	P-value
Age	−0.523 (−0.678 to −0.367)	−0.490	<0.001	−0.305 (−0.473 to −0.136)	−0.282	0.001
Male sex	−1.163 (−3.858 to 1.533)	−0.059	0.395	1.009 (−1.915 to 3.933)	0.050	0.496
BMI	−0.603 (−0.991 to −0.215)	−0.231	0.003	−0.751 (−1.172 to −0.330)	−0.284	0.001
Fasting glucose	−0.081 (−0.260 to 0.097)	−0.067	0.369	−0.112 (−0.306 to 0.081)	−0.091	0.254
Triglycerides	−0.010 (−0.067 to 0.047)	−0.025	0.732	−0.053 (−0.115 to 0.009)	−0.135	0.091

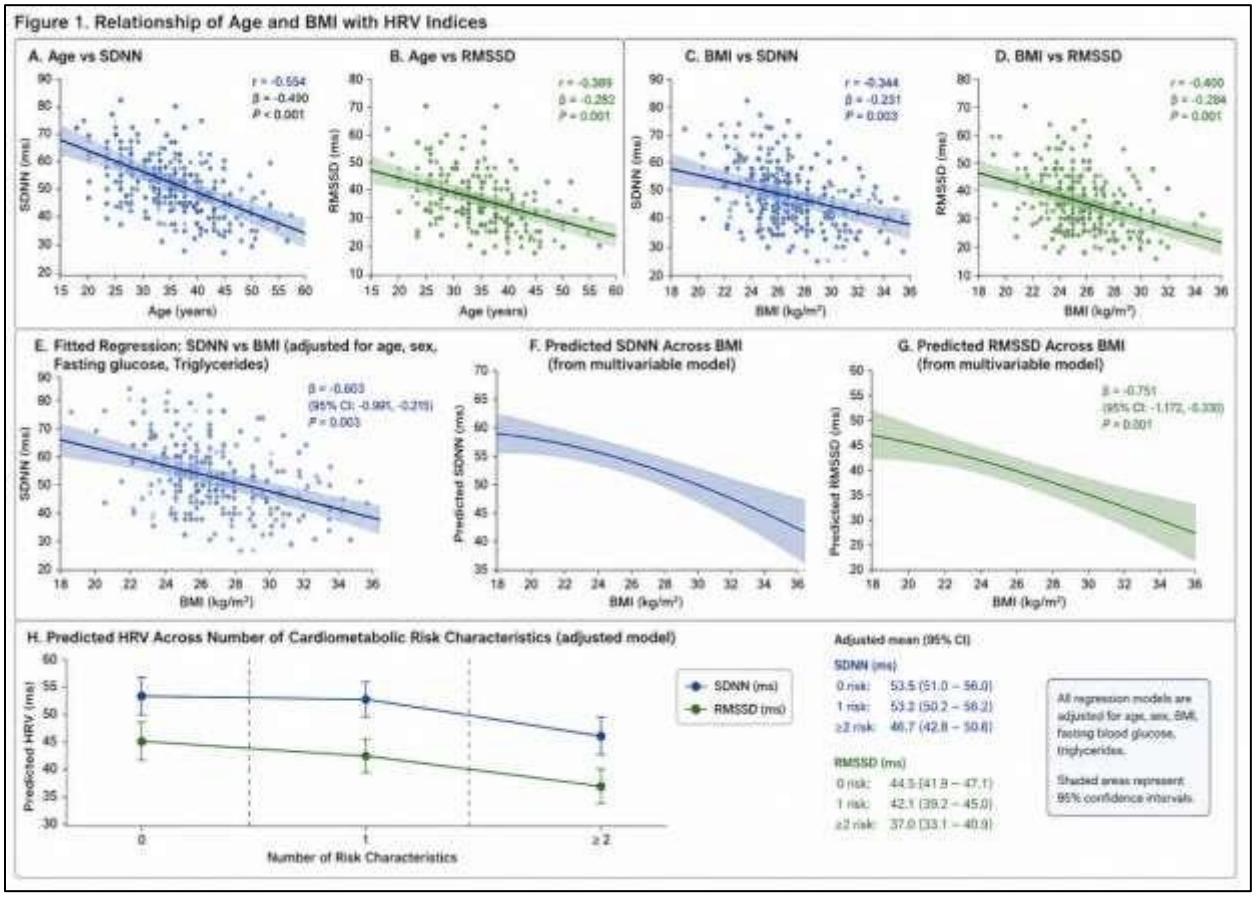
Model statistics: SDNN: $R^2 = 0.379$, adjusted $R^2 = 0.355$, $P < 0.001$. RMSSD: $R^2 = 0.288$, adjusted $R^2 = 0.261$, $P < 0.001$.

B = unstandardized regression coefficient; β = standardized regression coefficient; CI = confidence interval; BMI = body mass index.

Integrated cardiometabolic–autonomic phenotype

Taken together, the analyses demonstrated a consistent relationship between cardiometabolic phenotype and cardiac autonomic variability. Age and adiposity showed the strongest associations with HRV, while fasting glucose, triglycerides, waist circumference, and systolic blood pressure contributed additional univariate relationships. Importantly, clustering of two or more cardiometabolic risk characteristics was associated with significantly lower SDNN and RMSSD compared with the metabolically more favorable phenotype.

Multivariable analysis further identified age and BMI as the principal independent determinants of autonomic variability. These findings demonstrate measurable heterogeneity in cardiac autonomic regulation across cardiometabolic phenotypes and support the presence of an unfavorable autonomic phenotype accompanying accumulation of cardiometabolic abnormalities.



DISCUSSION

The present study demonstrated a consistent relationship between cardiac autonomic variability and cardiometabolic phenotype among apparently healthy adults. Lower SDNN and RMSSD were associated with several unfavorable cardiometabolic characteristics, particularly increasing age, adiposity, fasting glucose, and triglyceride concentrations. More importantly, participants exhibiting clustering of two or more cardiometabolic risk characteristics showed substantially lower HRV than those with a more favorable phenotype. Multivariable analysis further identified age and BMI as the principal independent determinants of autonomic variability. Collectively, these findings suggest that alterations in cardiac autonomic regulation may accompany early cardiometabolic dysregulation even before clinically established metabolic or cardiovascular disease becomes apparent.

The reduction in HRV observed with increasing cardiometabolic burden is consistent with evidence linking metabolic syndrome to impaired autonomic regulation. Both short- and long-term HRV studies have demonstrated differences between individuals with and without metabolic syndrome, indicating that clustering of metabolic abnormalities is accompanied by measurable changes in autonomic cardiac control (Ortiz-Guzmán et al., 2023a; Ortiz-Guzmán et al., 2023b). In the present analysis, the distinction was particularly evident when participants with two or more risk characteristics were compared with those without identified abnormalities. SDNN decreased from 53.51 ms in the zero-risk phenotype to 46.68 ms in the ≥2-risk phenotype, while RMSSD declined from 44.54 to 37.00 ms. This pattern suggests that autonomic alteration may become more apparent when multiple components of an adverse cardiometabolic phenotype coexist rather than when an isolated risk characteristic is present.

The phenotype-based approach is particularly relevant because cardiometabolic dysfunction develops through interacting biological systems rather than through isolated abnormalities. Adiposity, glucose regulation, lipid metabolism, vascular function, and autonomic activity are physiologically interconnected. Increased sympathetic activation and reduced parasympathetic modulation have been implicated in obesity and metabolic dysfunction, while altered autonomic regulation may itself influence energy expenditure, vascular tone, glucose metabolism, and

cardiovascular homeostasis. Consequently, reduced HRV may represent an integrated physiological expression of cardiometabolic dysregulation rather than a disease-specific abnormality.

Adiposity emerged as one of the most consistent determinants of the autonomic phenotype in the present study. BMI correlated inversely with both SDNN and RMSSD, and importantly, these relationships were not entirely explained by other measured cardiometabolic variables. After multivariable adjustment, BMI remained independently associated with SDNN ($\beta = -0.231$, $P = 0.003$) and RMSSD ($\beta = -0.284$, $P = 0.001$). The stronger association with RMSSD may be particularly relevant because RMSSD predominantly reflects short-term parasympathetic modulation. Previous evidence has similarly linked overweight and obesity with altered HRV, while physical activity and weight reduction may favorably influence cardiac autonomic control (Mattos et al., 2022; Sinha et al., 2023). These observations support adiposity as an important component of the biological interface between metabolic phenotype and autonomic regulation.

Several mechanisms may plausibly contribute to this relationship. Adipose tissue functions as an active endocrine and metabolic organ, and increasing adiposity is associated with altered adipokine signaling, chronic low-grade inflammation, insulin resistance, oxidative stress, and changes in sympathetic nervous system activity. These interacting pathways may modify sinoatrial autonomic modulation and thereby influence beat-to-beat cardiovascular variability. The present study did not directly measure inflammatory mediators, adipokines, oxidative stress, insulin resistance, or molecular signaling pathways; therefore, these mechanisms cannot be established from the current findings. Nevertheless, the persistence of the BMI–HRV relationship after adjustment supports further investigation of the biological pathways linking adiposity to cardiac autonomic phenotype.

Age represented the strongest independent determinant of SDNN and was also independently associated with RMSSD. In the adjusted models, increasing age was associated with lower SDNN ($\beta = -0.490$, $P < 0.001$) and RMSSD ($\beta = -0.282$, $P = 0.001$). Age-related alterations in autonomic regulation may reflect changes in parasympathetic responsiveness, cardiovascular adaptability, baroreflex function, and neurohumoral regulation. HRV is known to vary considerably with demographic and physiological characteristics, making age an important consideration when interpreting autonomic phenotypes. Recent work in healthy adults has likewise emphasized the importance of age, sex, BMI, and physical activity when evaluating resting autonomic and cardiovascular function (Alyahya et al., 2024). The strong age effect observed in the present study therefore reinforces the need to interpret HRV within an integrated physiological context rather than according to a single universal threshold.

The relationships with glycemic and lipid characteristics provide additional insight. Fasting blood glucose was inversely correlated with both SDNN and RMSSD, while triglyceride concentration was similarly associated with lower values of both HRV indices. HDL-C showed a positive relationship with SDNN. These findings initially suggest that deterioration in glucose and lipid phenotype accompanies reduced autonomic variability. However, fasting glucose and triglycerides did not remain statistically significant independent predictors after multivariable adjustment. This distinction is important. Rather than indicating that glucose and triglycerides have no relationship with autonomic function, the adjusted findings suggest that their associations with HRV may partly reflect shared biological relationships with age, adiposity, or other components of the cardiometabolic phenotype.

The contrast between correlation and multivariable analysis also supports interpretation of cardiometabolic characteristics as an interconnected phenotype. Conventional risk factors frequently cluster, and the biological pathways connecting them are not independent. Adiposity can influence insulin sensitivity, circulating triglycerides, blood pressure, inflammatory signaling, and autonomic activity simultaneously. The attenuation of glucose and triglyceride associations after adjustment may therefore indicate overlapping physiological pathways rather than absence of metabolic relevance. This interpretation is also compatible with meta-analytic evidence demonstrating autonomic abnormalities at the level of the overall metabolic syndrome phenotype (Ortiz-Guzmán et al., 2023a; Ortiz-Guzmán et al., 2023b).

RMSSD appeared particularly responsive to cumulative cardiometabolic burden. Participants with ≥2 risk characteristics had significantly lower RMSSD than participants with no identified risk characteristics. Because RMSSD is predominantly influenced by vagally mediated beat-to-beat variation, this finding may suggest that parasympathetic modulation is altered as the cardiometabolic phenotype becomes less favorable. SDNN also declined significantly in the ≥2-risk phenotype, indicating that the observed pattern was not restricted to a single HRV measure. The parallel reduction of SDNN and RMSSD strengthens the overall evidence for altered cardiac autonomic regulation across increasingly unfavorable cardiometabolic phenotypes.

An important feature of the present study is that these relationships were examined among adults considered apparently healthy rather than among patients selected because of established diabetes, hypertension, cardiovascular disease, or metabolic syndrome. This distinction has potential biological significance. Cardiometabolic disease represents a continuum, and physiological alterations may develop before conventional diagnostic thresholds are crossed. Apparently healthy populations may consequently contain individuals with substantially different metabolic and autonomic phenotypes. Identifying these differences may improve understanding of the early transition from metabolic homeostasis toward clinically recognizable cardiometabolic dysfunction.

The findings may also have particular relevance in populations with a substantial background burden of metabolic risk. Evidence from Pakistan indicates that cardiometabolic abnormalities and metabolic syndrome are common even among adults considered apparently healthy (Adil et al., 2023). Within such populations, assessment of physiological phenotypes may complement conventional anthropometric and biochemical measurements by providing information about functional cardiovascular regulation. HRV should not be regarded as a replacement for established cardiometabolic risk assessment; rather, it may represent an additional physiological dimension of the cardiometabolic phenotype.

The potentially modifiable nature of autonomic function further increases the biological relevance of these findings. Exercise, improved physical fitness, and weight reduction have been associated with favorable changes in HRV in overweight and obese populations (Mattos et al., 2022; Sinha et al., 2023). Such observations suggest that autonomic phenotype may not simply reflect fixed susceptibility but may respond to changes in metabolic and behavioral characteristics. Longitudinal studies are needed to determine whether improvement in cardiometabolic phenotype is accompanied by corresponding normalization of SDNN and RMSSD and whether these changes predict subsequent clinical outcomes.

Several limitations should be considered. The cross-sectional design does not permit determination of temporal or causal relationships between cardiometabolic characteristics and autonomic variability. HRV was assessed using a short-term resting recording and may not capture all dimensions of autonomic regulation measurable using prolonged or frequency-domain assessment. Although major confounding variables were considered, residual effects of diet, sleep, psychological stress, cardiorespiratory fitness, respiration, and other behavioral or physiological factors cannot be excluded. In addition, classification according to cumulative risk burden simplifies a biologically heterogeneous phenotype, as different combinations of abnormalities may have different autonomic consequences. Finally, molecular mediators potentially linking cardiometabolic dysfunction with altered autonomic regulation were not directly measured.

Despite these limitations, the integrated analysis of anthropometric, hemodynamic, biochemical, and autonomic characteristics provides evidence that cardiac autonomic variability differs across cardiometabolic phenotypes even in the absence of clinically established disease. The independent associations of age and BMI with both major HRV indices, together with the reduction in SDNN and RMSSD among participants with multiple cardiometabolic abnormalities, support a close relationship between metabolic phenotype and autonomic regulation. Future studies incorporating longitudinal follow-up and molecular measures of inflammation, adipose-tissue signaling, oxidative stress, insulin resistance, and related regulatory pathways could clarify the mechanisms underlying this relationship and determine whether HRV contributes to characterization of early cardiometabolic dysfunction.

CONCLUSION

Cardiac autonomic variability was closely associated with cardiometabolic phenotype among apparently healthy adults. Lower SDNN and RMSSD accompanied increasing adiposity, age, and less favorable glycemic and lipid characteristics, while clustering of two or more cardiometabolic risk characteristics was associated with substantially reduced HRV. After multivariable adjustment, age and BMI emerged as the principal independent determinants of both SDNN and RMSSD, suggesting that aging and adiposity are particularly important contributors to variation in cardiac autonomic regulation.

These findings support the concept that autonomic dysregulation may form part of the broader physiological phenotype accompanying early cardiometabolic deterioration, even before clinically established disease becomes apparent. HRV may therefore provide a complementary functional measure for characterizing early cardiometabolic dysfunction. Longitudinal studies integrating HRV with molecular markers of inflammation, insulin resistance, oxidative stress, and adipose-tissue signaling are warranted to clarify underlying biological mechanisms and determine the potential predictive significance of the cardiometabolic–autonomic phenotype.

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Authors' Contributions

All authors contributed substantially to the conception and design of the study, acquisition and/or interpretation of data, and preparation of the manuscript. All authors critically reviewed the manuscript for important intellectual content and approved the final version for submission. Specific author contributions will be assigned according to the final authorship order.

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Conflict of Interest
The authors declare **no conflict of interest** related to this study.

Data Availability
The data supporting the findings of this study are available from the corresponding author upon reasonable request and subject to applicable institutional and ethical requirements.

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