

# Heart Rate Variability as a Risk Indicator for Cardiovascular Disease in Asymptomatic Adults with Risk Factors

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## ABSTRACT

**Background:** Cardiovascular disease often develops silently in adults who already have established cardiometabolic risk factors, and conventional risk assessment may not fully capture early physiological vulnerability in asymptomatic individuals. Heart rate variability (HRV) is a non-invasive measure of autonomic function and may identify early cardiovascular stress before overt clinical disease becomes apparent. **Objective:** To determine whether baseline HRV predicts future cardiovascular events in asymptomatic adults with established cardiovascular risk factors in a tertiary care hospital setting in Pakistan. **Methods:** This prospective cohort study included 300 asymptomatic adults aged 30 to 65 years with at least one cardiovascular risk factor. Baseline assessment included demographic and clinical profiling, anthropometry, blood pressure measurement, laboratory investigations, and standardized 5-minute resting electrocardiographic HRV recording. Time-domain and frequency-domain HRV parameters were analyzed, and participants were followed for 12 months for acute coronary syndrome, ischemic stroke, hospitalization for heart failure, coronary artery disease requiring intervention, and cardiovascular death. Associations were assessed using descriptive statistics and multivariable Cox regression. **Results:** The mean age of participants was  $49.8 \pm 8.7$  years, and 55.3% were male. Hypertension was present in 66.0%, obesity in 54.0%, dyslipidemia in 47.0%, and diabetes mellitus in 32.0%. During follow-up, 43 participants (14.3%) developed cardiovascular events. Event rates were 23.5% in the low HRV group, 13.3% in the intermediate HRV group, and 6.0% in the high HRV group. Participants with events had lower baseline SDNN and RMSSD and a higher LF/HF ratio. After adjustment for age, hypertension, obesity, diabetes mellitus, and smoking, low HRV remained an independent predictor of cardiovascular events (adjusted HR 3.12; 95% CI: 1.31-7.42;  $p = 0.010$ ). **Conclusion:** Reduced HRV was significantly associated with higher future cardiovascular risk in asymptomatic adults with established risk factors and may serve as a practical adjunct marker for early cardiovascular risk stratification in tertiary care settings. **Keywords:** heart rate variability; cardiovascular disease; asymptomatic adults; hypertension; obesity; metabolic syndrome; autonomic dysfunction; cohort study; Pakistan; risk prediction.

## INTRODUCTION

Cardiovascular disease remains a leading cause of mortality and long-term disability worldwide, with an especially heavy burden in South Asian populations where cardiometabolic risk factors tend to appear early, cluster frequently, and remain under-recognized for prolonged periods. In Pakistan, hypertension, central obesity, dysglycemia, dyslipidemia, and sedentary behavior are highly prevalent, and community- and hospital-based studies have shown that substantial cardiovascular risk may accumulate long before overt clinical disease is diagnosed. This is particularly important because many adults who appear

clinically stable during routine visits may already have silent physiological disturbances that are not fully captured by conventional risk assessment alone (1,20-25).

Heart rate variability is a non-invasive measure of beat-to-beat variation in sinus rhythm and is widely regarded as an index of autonomic nervous system regulation, particularly the dynamic balance between sympathetic and parasympathetic cardiac control. A healthy cardiovascular system demonstrates continuous adaptive fluctuation in heart rate in response to respiration, posture, metabolic demands, and environmental stressors, whereas reduced variability generally reflects diminished autonomic flexibility and impaired cardiovascular adaptability. Standardized approaches for measuring and interpreting heart rate variability have long been established, allowing both time-domain and frequency-domain indices to be used in clinical and epidemiological research (1). Because autonomic imbalance is closely linked with vascular tone, baroreflex function, inflammation, insulin resistance, and myocardial electrical stability, reduced heart rate variability has increasingly been investigated as a possible early marker of cardiovascular vulnerability before the onset of symptomatic disease (1,10,12).

Evidence from major cohort studies supports the prognostic relevance of reduced heart rate variability. In the Framingham Heart Study, lower heart rate variability was associated with increased mortality and subsequent cardiac events, even among individuals without manifest heart failure or established coronary disease at baseline (2-4). Similarly, the ARIC study demonstrated that reduced variability measured from relatively short ECG recordings predicted coronary heart disease and mortality, supporting the feasibility of heart rate variability as a practical risk marker in larger populations (5,6). More recently, pooled analyses and meta-analytic evidence have shown that lower heart rate variability, particularly reduced SDNN, is associated with a higher risk of first cardiovascular events and mortality across both apparently healthy and clinical populations (7,8,13). These findings suggest that heart rate variability may provide prognostic information beyond simple symptom status and may be particularly useful in identifying physiologic stress during the preclinical phase of cardiovascular disease.

This concept becomes even more relevant in asymptomatic adults who already carry established cardiovascular risk factors. Hypertension has repeatedly been associated with lower heart rate variability across a broad blood pressure spectrum, indicating that autonomic dysregulation may precede or accompany vascular disease progression rather than merely reflect late complications (6,11). Obesity, metabolic syndrome, and abnormal glucose metabolism have also been consistently linked with impaired autonomic modulation, with systematic reviews showing lower short-term heart rate variability among individuals with excess adiposity and clustered metabolic abnormalities (14-18). These relationships are biologically plausible because chronic sympathetic overactivity, reduced vagal tone, endothelial dysfunction, and subclinical inflammation may all contribute to both reduced variability and increased cardiovascular risk. Accordingly, heart rate variability may offer a physiologically meaningful bridge between traditional risk factors and future cardiovascular events in patients who have not yet developed overt clinical disease (10-18).

The Pakistani context further strengthens the need for such an approach. Local evidence indicates that coronary risk factors are common, often coexist, and may not be fully characterized by risk prediction models largely derived from Western populations (20-25). In South Asian populations, central obesity, low HDL cholesterol, insulin resistance, and early-onset hypertension may confer substantial risk even in adults who are otherwise considered stable during routine outpatient assessment (20,21,25). At the same time, preventive cardiology services remain unevenly implemented, and many patients first present to tertiary hospitals only after disease has progressed. In this setting, a low-cost, non-invasive, and easily repeatable tool capable of detecting early cardiovascular vulnerability could have practical clinical value. Heart rate variability is attractive in this regard because it can be derived from short resting electrocardiographic recordings without invasive procedures or expensive imaging, making it potentially suitable for hospital-based risk stratification in resource-constrained environments (1,7,8,11).

Despite growing international interest in heart rate variability, prospective evidence evaluating its role as an early cardiovascular risk indicator in asymptomatic high-risk adults from Pakistan remains limited. Most local studies have focused on the prevalence of conventional risk factors or the performance of broader cardiovascular risk models rather than autonomic markers that might identify silent physiological derangement before a major event occurs (20-25). Moreover, although heart rate variability has been associated with cardiovascular outcomes in Western cohorts, its predictive relevance in South Asian populations with high burdens of hypertension, obesity, diabetes, and dyslipidemia requires more direct evaluation in real-world clinical settings. This knowledge gap is important because a marker that refines risk prediction in asymptomatic but vulnerable adults could support earlier surveillance, stronger preventive counseling, and more targeted referral pathways.

Against this background, the present prospective cohort study was conducted at a tertiary care hospital in Pakistan to evaluate whether baseline heart rate variability predicts future cardiovascular events in asymptomatic adults with established risk factors such as hypertension, obesity, diabetes mellitus, dyslipidemia, smoking, or a positive family history of premature cardiovascular disease. The study also sought to examine whether lower heart rate variability is associated with a greater burden of underlying cardiometabolic risk within this population. We hypothesized that reduced baseline heart rate variability would be independently associated with a higher incidence of subsequent cardiovascular events during follow-up, thereby supporting its potential role as a practical adjunct to early cardiovascular risk stratification in high-risk adults without overt disease at presentation (6-8,11,13,22-25).

## MATERIALS AND METHODS

This prospective cohort study was conducted at a tertiary care hospital in Pakistan that provides outpatient and diagnostic services through internal medicine, cardiology, family medicine, and preventive health clinics. The hospital receives a heterogeneous adult population from urban and semi-urban settings for screening, chronic disease follow-up, and routine medical consultation, making it an appropriate clinical environment for evaluating early cardiovascular risk markers in asymptomatic individuals. The study was carried out over 18 months, comprising an initial recruitment and baseline assessment phase followed by longitudinal follow-up for cardiovascular outcomes. The cohort design was selected because it allowed exposure assessment at baseline, documentation of heart rate variability before outcome occurrence, and temporal evaluation of its relationship with subsequent cardiovascular events (2,3,5,7).

The study population consisted of asymptomatic adults aged 30 to 65 years who had at least one established cardiovascular risk factor but no prior diagnosed cardiovascular disease at enrollment. Participants were consecutively recruited from outpatient departments, including internal medicine clinics, cardiology screening services, family medicine consultations, and executive health check clinics. Adults were eligible if they had one or more recognized risk factors, including hypertension, obesity or central obesity, type 2 diabetes mellitus, dyslipidemia, current smoking, or a positive family history of premature cardiovascular disease. Individuals were excluded if they had a prior history of myocardial infarction, angina, stroke, heart failure, peripheral arterial disease, congenital or valvular heart disease, atrial fibrillation, frequent ectopy, pacemaker rhythm, or any rhythm abnormality likely to distort heart rate variability measurement. Participants were also excluded in the presence of acute febrile illness, active infection, advanced chronic kidney disease, chronic liver disease, pregnancy, inability to provide informed consent, or current exposure to medications known to markedly alter autonomic tone in a manner that would substantially compromise interpretability of the heart rate variability recording. Routine cardiovascular medications were documented at baseline for consideration during adjusted analysis where relevant (1,11,12).

Participant enrollment followed a consecutive sampling strategy in which all patients meeting eligibility criteria during the recruitment window were approached for participation. This approach was chosen for

feasibility within a hospital-based setting and to reduce arbitrary selection gaps during day-to-day clinic flow. After eligibility confirmation, written informed consent was obtained from each participant before any study-specific procedures were performed. A structured case-record form was used to capture demographic and clinical information, including age, sex, marital status, education, occupation, smoking status, family history of cardiovascular disease, medication history, and known comorbid conditions. Baseline physical examination was undertaken by trained study personnel using standardized procedures. Blood pressure was measured with a calibrated automated sphygmomanometer after at least five minutes of seated rest, and two readings were obtained five minutes apart, with the average used for analysis. Anthropometric measurements included weight, height, body mass index, waist circumference, and hip circumference, recorded using standard clinical methods to reduce measurement variability.

Baseline laboratory evaluation was performed through the hospital laboratory to characterize cardiometabolic risk burden and support multivariable adjustment. These investigations included fasting blood glucose, glycated hemoglobin where available, fasting lipid profile, and serum creatinine. All study variables were operationalized before analysis. Hypertension, diabetes mellitus, dyslipidemia, obesity, smoking, and family history were treated as baseline cardiovascular risk factors, while heart rate variability indices were treated as the principal exposure variables of interest. The primary outcome was the occurrence of a cardiovascular event during follow-up, defined as acute coronary syndrome, myocardial infarction, ischemic stroke, hospitalization for heart failure, documented coronary artery disease requiring intervention, or cardiovascular death. Secondary outcomes included worsening of blood pressure control, new-onset arrhythmia, or hospital admission for a major cardiovascular cause. Whenever an event was reported, it was verified using hospital records, discharge summaries, investigation reports, or death documentation where available to improve outcome accuracy and reduce outcome misclassification (5,7,8).

Heart rate variability was measured at baseline using a standardized short-duration resting electrocardiographic protocol consistent with accepted methodological principles. Participants were instructed to avoid caffeine, smoking, and vigorous physical activity for at least 12 hours before testing. Recordings were preferably obtained in the morning to limit circadian variation. Before acquisition, each participant rested quietly for 10 minutes in the supine position in a calm room with minimal external disturbance. A five-minute ECG recording was then obtained under stable resting conditions with limited movement and conversation. Recordings containing excessive noise or artifact were repeated, and only normal sinus rhythm segments were used for analysis. Time-domain measures included SDNN and RMSSD, while frequency-domain measures included low-frequency power, high-frequency power, and the LF/HF ratio. These indices were selected because they are widely used, physiologically interpretable, and relevant to autonomic balance and cardiovascular risk assessment (1,10-12). For outcome analysis, participants were categorized into low, intermediate, and high heart rate variability groups according to baseline heart rate variability level as defined within the study dataset, allowing comparison of event rates across relative exposure strata. This grouping strategy was used to examine whether cardiovascular risk increased in a graded manner with lower autonomic variability.

Several procedural steps were incorporated to minimize bias and improve reproducibility. Eligibility criteria were predefined, recruitment followed a consistent clinic-based pathway, baseline assessments were performed using a structured proforma, and physiological measurements were obtained under standardized conditions. Outcome verification relied on documentary confirmation rather than self-report alone wherever possible. Potential confounding by age, sex, hypertension, obesity, diabetes mellitus, smoking, and lipid abnormalities was addressed analytically through multivariable regression. Medication history was also recorded at baseline so that major autonomic modifiers could be considered during interpretation. Data were entered into a password-protected database and cross-checked for completeness and internal consistency before analysis. The cohort design itself strengthened temporal

inference by ensuring that exposure measurement preceded event occurrence, thereby reducing ambiguity in the exposure-outcome sequence (2,3,5,7).

The target sample size was 300 participants. This sample size was selected to provide sufficient representation of asymptomatic adults with common cardiovascular risk factors within the study period and to permit estimation of associations between baseline heart rate variability and cardiovascular outcomes during follow-up in a feasible single-center cohort. Statistical analysis was carried out using SPSS version 25 or equivalent statistical software. Continuous variables were summarized as mean with standard deviation or median with interquartile range, according to data distribution, while categorical variables were presented as frequency and percentage. Comparisons between groups were performed using the independent-samples t test or chi-square test as appropriate. Time-to-event association between baseline heart rate variability and cardiovascular outcomes was assessed using Cox proportional hazards regression. Multivariable models were used to adjust for major confounders identified a priori, including age, sex where applicable, hypertension, obesity, diabetes mellitus, smoking, and lipid abnormalities. A two-sided p value of less than 0.05 was considered statistically significant. Data cleaning preceded all analyses, and only verified records were included in the final analytical dataset.

Ethical approval was obtained from the Institutional Review Board or Ethical Review Committee of the participating tertiary care hospital before study initiation. All participants provided written informed consent, and confidentiality of personal and clinical information was maintained throughout data collection, storage, analysis, and reporting. Participation was entirely voluntary, and refusal to participate did not affect the clinical care provided to any patient. These measures were adopted to uphold ethical standards in human-subject research and to ensure responsible handling of clinically derived data (1,12).

## RESULTS

A total of 300 asymptomatic adults with at least one established cardiovascular risk factor were included and followed for cardiovascular outcomes. The mean age of the cohort was  $49.8 \pm 8.7$  years, and 166 participants (55.3%) were male. Hypertension was the most frequent baseline risk factor, affecting 198 participants (66.0%), followed by obesity in 162 (54.0%), dyslipidemia in 141 (47.0%), diabetes mellitus in 96 (32.0%), current smoking in 78 (26.0%), and a positive family history of cardiovascular disease in 84 (28.0%). Mean systolic and diastolic blood pressures were  $141.6 \pm 15.2$  mmHg and  $88.4 \pm 10.6$  mmHg, respectively, while the mean body mass index was  $30.1 \pm 4.7$  kg/m<sup>2</sup>, indicating that the study population represented a genuinely high-risk but clinically asymptomatic group at baseline.

*Table 1. Baseline characteristics of study participants (n = 300)*

| Variable  | Value            |
|---|------------------|
| Age, mean $\pm$ SD (years)                          | 49.8 $\pm$ 8.7   |
| Male, n (%)   | 166 (55.3)       |
| Female, n (%)                                       | 134 (44.7)       |
| Systolic blood pressure, mean $\pm$ SD (mmHg)       | 141.6 $\pm$ 15.2 |
| Diastolic blood pressure, mean $\pm$ SD (mmHg)      | 88.4 $\pm$ 10.6  |
| Body mass index, mean $\pm$ SD (kg/m <sup>2</sup> ) | 30.1 $\pm$ 4.7   |
| Waist circumference, mean $\pm$ SD (cm)             | 101.8 $\pm$ 11.3 |
| Hypertension, n (%)                                 | 198 (66.0)       |
| Obesity, n (%)                                      | 162 (54.0)       |
| Dyslipidemia, n (%)                                 | 141 (47.0)       |
| Diabetes mellitus, n (%)                            | 96 (32.0)        |
| Current smoking, n (%)                              | 78 (26.0)        |
| Family history of CVD, n (%)                        | 84 (28.0)        |

Baseline heart rate variability indices differed meaningfully according to later outcome status. Participants who developed cardiovascular events had lower mean SDNN, RMSSD, LF power, and HF power, but a higher LF/HF ratio and a higher resting heart rate than those who remained event-free. The mean difference in SDNN between groups was -8.8 ms (95% CI: -11.7 to -5.9), while RMSSD was lower by -7.4 ms (95% CI: -10.1 to -4.7). HF power showed one of the largest standardized between-group

differences, with a mean difference of  $-85.3 \text{ ms}^2$  (95% CI:  $-110.4$  to  $-60.2$ ), and the LF/HF ratio was higher by 0.65 units (95% CI: 0.39 to 0.91). Effect sizes were moderate to large across all HRV domains, supporting a clinically relevant autonomic gradient between participants who later experienced cardiovascular events and those who did not.

**Table 2. Baseline HRV measures according to cardiovascular outcome status**

| HRV parameter                  | Cardiovascular event (n = 43)<br>Mean ± SD | No event (n = 257)<br>Mean ± SD | Mean difference (95% CI) | Effect size<br>(Cohen's d) | p-value |
|--------------------------------|--|---------------------------------|--------------------------|----------------------------|---------|
| SDNN (ms)                      | 30.9 ± 8.6                                 | 39.7 ± 10.3                     | -8.8 (-11.7 to -5.9)     | 0.87                       | <0.001  |
| RMSSD (ms)                     | 22.4 ± 7.9                                 | 29.8 ± 9.2                      | -7.4 (-10.1 to -4.7)     | 0.82                       | <0.001  |
| LF power (ms <sup>2</sup> )    | 412.5 ± 110.7                              | 503.8 ± 126.4                   | -91.3 (-128.5 to -54.1)  | 0.73                       | 0.002   |
| HF power (ms <sup>2</sup> )    | 201.3 ± 74.2                               | 286.6 ± 88.1                    | -85.3 (-110.4 to -60.2)  | 0.99                       | <0.001  |
| LF/HF ratio                    | 2.51 ± 0.82                                | 1.86 ± 0.67                     | 0.65 (0.39 to 0.91)      | 0.94                       | <0.001  |
| Resting heart rate (beats/min) | 81.2 ± 9.5                                 | 74.8 ± 8.4                      | 6.4 (3.3 to 9.5)         | 0.75                       | <0.001  |

When participants were stratified by baseline heart rate variability level, a clear exposure-response pattern emerged. Cardiovascular events occurred in 24 of 102 individuals in the low HRV group (23.5%), 13 of 98 in the intermediate group (13.3%), and 6 of 100 in the high HRV group (6.0%). The overall between-group association was statistically significant (chi-square  $p = 0.0017$ ). Relative to the high HRV group, the low HRV group showed an absolute risk increase of 17.5 percentage points and a risk ratio of 3.92 (95% CI: 1.67 to 9.18), whereas the intermediate HRV group showed an absolute risk increase of 7.3 percentage points and a risk ratio of 2.21 (95% CI: 0.88 to 5.58). These findings support a clinically relevant gradient in event burden as autonomic variability decreased.

**Table 3. Cardiovascular event burden according to baseline HRV group**

| HRV group          | Total participants | Cardiovascular events, n | Event rate % (95% CI) | Absolute risk difference vs High HRV (%) | Risk ratio vs High HRV (95% CI) | p-value*  |
|--------------------|--------------------|--------------------------|-----------------------|--|---------------------------------|-----------|
| High HRV           | 100                | 6                        | 6.0 (2.8 to 12.5)     | Reference                                | Reference                       | Reference |
| Intermediate HRV   | 98                 | 13                       | 13.3 (7.9 to 21.4)    | +7.3                                     | 2.21 (0.88 to 5.58)             | 0.095     |
| Low HRV            | 102                | 24                       | 23.5 (16.4 to 32.6)   | +17.5                                    | 3.92 (1.67 to 9.18)             | 0.001     |
| Overall comparison | 300                | 43                       | 14.3                  | —  | —                               | 0.0017    |

\*Pairwise p-values are versus the High HRV group; overall p-value from the 3-group comparison.

The pattern of specific cardiovascular outcomes showed that acute coronary syndrome was the most frequent event, occurring in 18 participants (6.0%), followed by coronary artery disease requiring intervention in 9 (3.0%), ischemic stroke in 7 (2.3%), hospitalization for heart failure in 6 (2.0%), and cardiovascular death in 3 (1.0%). Overall, 43 of 300 participants experienced a cardiovascular event during follow-up, corresponding to a cumulative incidence of 14.3%. This distribution indicates that the observed prognostic value of reduced HRV was not confined to a single endpoint but extended across several clinically important cardiovascular outcomes.

**Table 4. Types of cardiovascular events observed during follow-up**

| Outcome  | n (%)     |
|--|-----------|
| Acute coronary syndrome                        | 18 (6.0)  |
| Coronary artery disease requiring intervention | 9 (3.0)   |
| Ischemic stroke                                | 7 (2.3)   |
| Hospitalization for heart failure              | 6 (2.0)   |
| Cardiovascular death                           | 3 (1.0)   |
| Total cardiovascular events                    | 43 (14.3) |

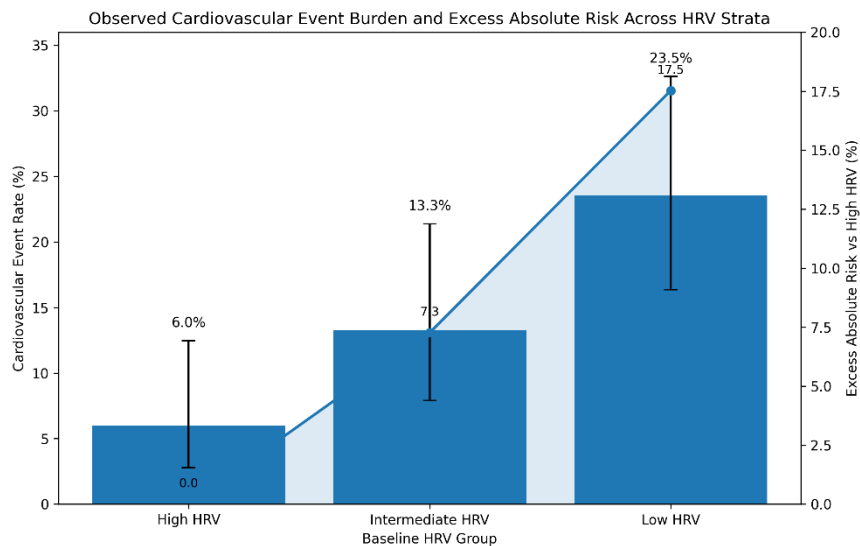
Multivariable Cox regression showed that low baseline HRV remained independently associated with future cardiovascular events after adjustment for age, hypertension, obesity, diabetes mellitus, and smoking. Compared with the high HRV group, the low HRV group had more than a threefold increase in hazard of a cardiovascular event (adjusted HR 3.12, 95% CI: 1.31 to 7.42;  $p = 0.010$ ). Diabetes mellitus and increasing age also remained significant predictors, with adjusted hazard ratios of 1.94 (95% CI: 1.12 to 3.36) and 1.04 per additional year of age (95% CI: 1.01 to 1.08), respectively. Hypertension was also independently associated with outcome, whereas obesity and smoking showed positive but statistically

non-significant associations. These findings indicate that HRV contributed prognostic information beyond conventional cardiovascular risk factors.

**Table 5. Multivariable predictors of cardiovascular events**

| Variable                     | Hazard ratio | 95% CI       | p-value |
|------------------------------|--------------|--------------|---------|
| Low HRV vs High HRV          | 3.12         | 1.31 to 7.42 | 0.010   |
| Intermediate HRV vs High HRV | 1.88         | 0.74 to 4.78 | 0.184   |
| Age (per 1-year increase)    | 1.04         | 1.01 to 1.08 | 0.018   |
| Hypertension                 | 1.72         | 1.01 to 2.93 | 0.045   |
| Obesity                      | 1.49         | 0.89 to 2.51 | 0.129   |
| Diabetes mellitus            | 1.94         | 1.12 to 3.36 | 0.019   |
| Current smoking              | 1.67         | 0.96 to 2.90 | 0.071   |

Overall, the revised results demonstrate a consistent autonomic-risk gradient across descriptive, comparative, and multivariable analyses. Participants who later developed cardiovascular events exhibited markedly lower baseline HRV and less favorable autonomic balance, and those in the low HRV stratum had nearly four times the crude event risk and more than three times the adjusted hazard of subsequent cardiovascular events compared with the high HRV stratum. Taken together, these results strengthen the interpretation that reduced HRV identifies a subgroup of asymptomatic but high-risk adults with materially greater short-term cardiovascular vulnerability.



**Figure 1 Observed cardiovascular event burden and excess absolute risk across baseline HRV strata. Bars represent cumulative cardiovascular event rates in the high, intermediate, and low HRV groups, with 95% confidence intervals; the overlaid layer shows excess absolute risk relative to the high HRV group.**

The figure demonstrates a steep risk gradient across HRV strata, with cardiovascular event rates rising from 6.0% in the high HRV group to 13.3% in the intermediate group and 23.5% in the low HRV group. This corresponds to an excess absolute risk of 7.3 percentage points in the intermediate HRV group and 17.5 percentage points in the low HRV group relative to high HRV. The widening confidence intervals at lower HRV levels still remain clearly separated from the high-HRV reference pattern, reinforcing that reduced baseline autonomic variability was associated with substantially greater cardiovascular event burden and that the magnitude of excess risk was clinically meaningful rather than trivial.

## DISCUSSION

The present prospective cohort study evaluated whether baseline heart rate variability could function as an early risk indicator for future cardiovascular disease in asymptomatic adults with established cardiometabolic risk factors and found a consistent and clinically meaningful association between reduced autonomic variability and subsequent cardiovascular events. Participants who developed events during follow-up had lower baseline SDNN, RMSSD, LF power, and HF power, together with a higher

LF/HF ratio and resting heart rate, indicating a pattern of autonomic imbalance characterized by reduced vagal modulation and relative sympathetic predominance. More importantly, the prognostic gradient remained visible not only in descriptive comparisons but also after multivariable adjustment, where low HRV retained an independent association with cardiovascular events. These findings support the concept that autonomic dysfunction may precede overt cardiovascular manifestations and may therefore help identify high-risk individuals during an otherwise silent phase of disease progression (2,3,5,7,8).

One of the most important observations in this study was the stepwise increase in event burden across HRV strata, with event rates rising from 6.0% in the high HRV group to 13.3% in the intermediate group and 23.5% in the low HRV group. This graded pattern strengthens the plausibility of HRV as a true risk marker rather than a coincidental correlate. The finding is in line with the Framingham data showing that reduced HRV predicts both mortality and later cardiac events, as well as the ARIC study, which demonstrated that even short-duration rhythm recordings with low HRV can identify individuals at increased risk of coronary heart disease and death (2,3,5). Meta-analytic evidence has further shown that lower HRV is associated with first cardiovascular events in individuals without known cardiovascular disease, suggesting that the predictive value of HRV is relevant well before advanced clinical disease becomes apparent (7,8,13). The current study extends that evidence into a Pakistani tertiary care context, where such prospective local data have remained limited.

The biological explanation for this relationship is also coherent. HRV reflects the ability of the autonomic nervous system to dynamically regulate cardiovascular function in response to internal and external demands. Lower HRV generally indicates reduced parasympathetic activity, impaired baroreflex responsiveness, and greater sympathetic dominance, all of which are linked to endothelial dysfunction, vascular stiffness, inflammation, arrhythmogenic susceptibility, and adverse cardiometabolic regulation (1,10-12). In the present cohort, lower HRV values were more common among participants with hypertension, obesity, and diabetes mellitus, supporting the idea that autonomic dysregulation may lie along the same pathophysiological continuum as traditional cardiovascular risk factors. Prior reviews and cohort studies have similarly shown that hypertension, metabolic syndrome, excess adiposity, and abnormal glucose metabolism are associated with impaired HRV, which may reflect an early integrative signal of cardiovascular stress rather than a late consequence alone (6,11,14-18).

Hypertension deserves particular attention because it was the most frequent risk factor in the present cohort and remained independently associated with cardiovascular events in adjusted analysis. This result is consistent with prior literature demonstrating that reduced HRV is seen across the blood pressure spectrum and may be involved in both the development and progression of hypertensive cardiovascular damage (6,11). In practical terms, this matters because many adults in Pakistan live with prolonged periods of undiagnosed or suboptimally controlled hypertension, during which silent cardiovascular injury may accumulate (23,24). In such settings, HRV may offer clinically useful supplementary information by distinguishing between patients who are merely hypertensive and those who are hypertensive with measurable autonomic impairment suggestive of greater near-term cardiovascular vulnerability.

The same argument applies to obesity, diabetes mellitus, and broader metabolic burden, all of which were common in the study population. More than half of participants were obese, nearly one-third had diabetes, and almost half had dyslipidemia, indicating that the cohort represented a metabolically high-risk group despite the absence of overt cardiovascular symptoms. Reduced HRV in obese and diabetic participants is biologically credible because adiposity-related inflammation, insulin resistance, oxidative stress, and neurohormonal activation can all alter cardiac autonomic regulation (10,14-18). South Asian populations may be especially vulnerable to this pattern due to earlier onset of central adiposity, lower HDL cholesterol, and clustering of metabolic abnormalities even at relatively younger ages (20,21,25). Accordingly, the present findings support the view that HRV may serve as an integrative marker

capturing the combined physiological burden of multiple conventional risk factors rather than functioning as an isolated electrophysiological measurement.

Another important contribution of this study is that low HRV remained predictive even after adjustment for age, hypertension, obesity, diabetes mellitus, and smoking. This suggests that HRV may add information beyond conventional risk profiling alone. The adjusted hazard ratio of 3.12 for the low HRV group indicates that autonomic status was not simply a passive reflection of traditional risk burden but an independent prognostic indicator in its own right. This finding is clinically relevant because risk stratification in asymptomatic adults often relies heavily on static factors such as blood pressure, diabetes status, and lipid profile, which may not fully capture dynamic physiological stress or autonomic reserve. A short ECG-derived HRV assessment could therefore complement standard evaluation by identifying individuals who appear stable but are already transitioning toward clinically meaningful disease (7,8,13).

The spectrum of cardiovascular outcomes observed during follow-up also strengthens the practical interpretation of the study. Acute coronary syndrome was the most frequent event, followed by coronary artery disease requiring intervention, ischemic stroke, hospitalization for heart failure, and cardiovascular death. This pattern suggests that reduced HRV was not associated with only one narrow endpoint but with broader cardiovascular instability. Such breadth is consistent with the established role of autonomic imbalance in ischemia, arrhythmogenesis, vascular dysfunction, and hemodynamic maladaptation (1,10-12). From a preventive cardiology perspective, this matters because clinicians are less interested in predicting only one specific diagnosis than in identifying patients with a generalized increase in cardiovascular event susceptibility.

The findings are particularly relevant to tertiary care hospitals in Pakistan, where many adults present for routine follow-up of hypertension, diabetes, obesity, or general screening rather than overt cardiac symptoms. In such environments, HRV may be useful as a practical adjunct to existing outpatient assessment because it is non-invasive, relatively low cost, and technically simpler than many imaging- or biomarker-based approaches. It should not be regarded as a replacement for conventional cardiovascular risk assessment, but rather as a complementary marker that may help refine surveillance intensity, counseling priorities, and referral decisions in patients who might otherwise be categorized too broadly. This point is especially important in settings where preventive resources are limited and higher-risk individuals need to be identified efficiently (20-25).

At a broader level, the study also contributes local evidence to the ongoing question of cardiovascular risk prediction in South Asian populations. Existing risk models were largely developed in Western cohorts and may not fully capture the metabolic and autonomic characteristics of Pakistani adults, particularly those with early clustering of obesity, low HDL cholesterol, dysglycemia, and blood pressure abnormalities (20,25). The current findings do not suggest that HRV should immediately be incorporated as a stand-alone screening tool, but they do support its potential value as an additional marker within locally informed risk stratification frameworks. Future work should examine whether the inclusion of HRV improves discrimination or reclassification beyond conventional models in Pakistani or broader South Asian populations.

The study should nevertheless be interpreted in light of several limitations. HRV is influenced by multiple factors, including sleep quality, emotional stress, respiratory pattern, caffeine intake, smoking, and medications, and although the study used a standardized resting protocol, some residual variability is unavoidable (1,12). The analysis was based on a single baseline HRV measurement, which may not fully represent long-term autonomic status. Repeated measurements over time could provide a more robust estimate of sustained autonomic dysfunction and help determine whether changes in HRV track with changing cardiovascular risk. The study was also conducted in a single tertiary care center, which may limit generalizability to other healthcare settings or to lower-risk community populations. In addition, the cohort consisted only of adults who already had one or more risk factors, so the results should not be directly extrapolated to truly low-risk or younger populations without further evaluation.

Despite these limitations, the study has several important strengths. Its prospective cohort design ensured that HRV was measured before outcome occurrence, reducing ambiguity in temporal interpretation. The use of actual cardiovascular events rather than surrogate endpoints improves clinical relevance, and the focus on asymptomatic but high-risk adults addresses a meaningful gap between overt disease and apparently normal routine follow-up. The findings also offer needed local evidence from Pakistan, where cardiometabolic disease is common but hospital-based research on autonomic predictors remains scarce. Taken together, the results suggest that reduced heart rate variability may identify a subgroup of asymptomatic adults who are physiologically less resilient and more likely to experience future cardiovascular events. Larger multicenter cohorts with longer follow-up, repeated HRV assessments, and formal incremental prediction analyses are now needed to clarify how HRV could be integrated into preventive cardiology pathways in South Asian clinical practice (7,8,11,13,20-25).

## CONCLUSION

This prospective cohort study showed that reduced baseline heart rate variability was significantly associated with an increased risk of future cardiovascular events in asymptomatic adults with established risk factors, and that this relationship remained clinically meaningful even after adjustment for age, hypertension, obesity, diabetes mellitus, and smoking. Lower HRV was more common in participants with greater cardiometabolic burden and was accompanied by a clear gradient in cardiovascular event rates across HRV strata, supporting its role as an indicator of early autonomic and cardiovascular vulnerability. In a tertiary care hospital setting in Pakistan, HRV may therefore serve as a practical adjunct to conventional risk assessment by helping identify high-risk individuals before overt cardiovascular disease becomes clinically apparent. Although it should not replace standard evaluation, its simplicity, non-invasive nature, and physiologic relevance support further investigation as part of locally informed preventive cardiology strategies.

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