# Original Article

# The role of sleep and heart rate variability in metabolic syndrome: evidence from the Midlife in the United States study

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## Abstract

**Study Objectives:** Poor sleep and autonomic dysregulation can both disrupt metabolic processes. This study examined the individual and combined effects of poor sleep and reduced heart rate variability (HRV) on metabolic syndrome among 966 participants in the Midlife in the United States II (MIDUS II) study.
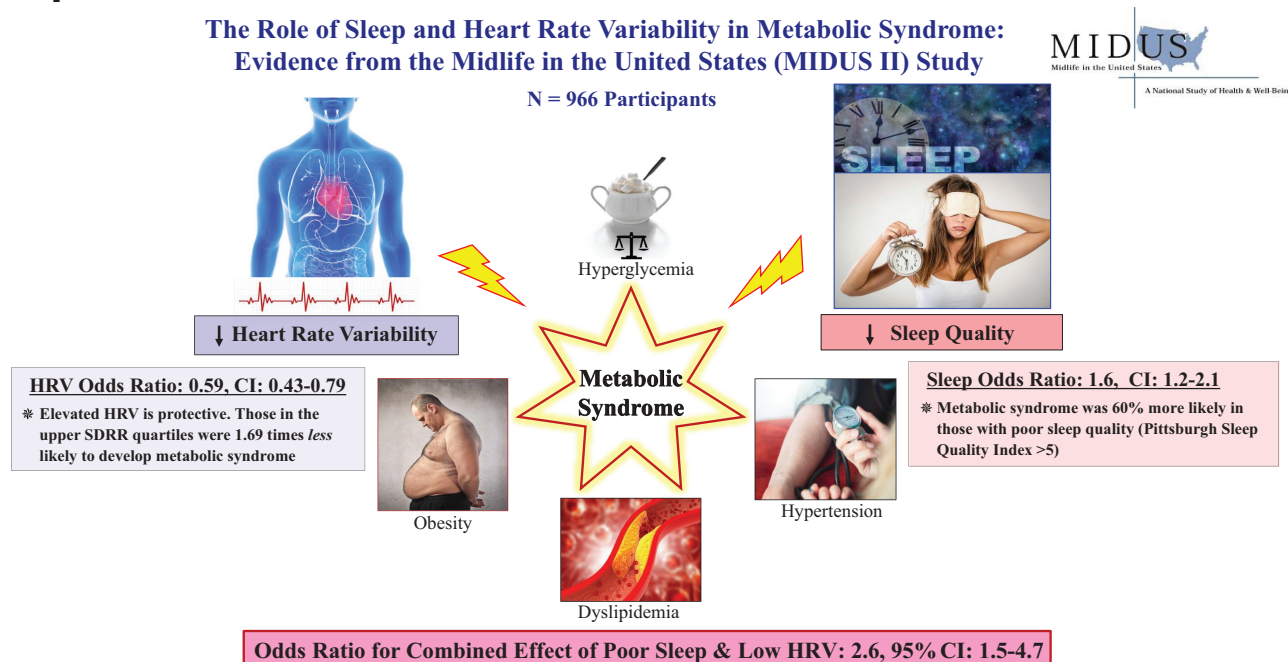
**Methods:** Self-reported sleep was assessed using the Pittsburgh Sleep Quality Index (PSQI). HRV was acquired from 11-minute resting heart rate recordings. Spearman correlations, general linear regression, and logistic regression models were used to examine the study hypotheses.

**Results:** Poor sleep quality was associated with metabolic syndrome when global PSQI scores were evaluated as a continuous (odds ratio [OR]: 1.07, 95% confidence interval [CI]: 1.03 to 1.11) or categorical measure (cutoff > 5, OR: 1.58, 95% CI: 1.19 to 2.10), after adjustment for confounding. There also was an association between reduced HRV and metabolic syndrome (ln [HF-HRV] OR: 0.89, 95% CI: 0.80 to 0.99; ln [LF-HRV] OR: 0.82, 95% CI: 0.72 to 0.92; ln [SDRR] OR: 0.59, 95% CI: 0.43 to 0.79; ln [RMSSD] OR: 0.75, 95% CI: 0.60 to 0.94). When the combined effects of poor sleep and low HRV were examined, the association with metabolic syndrome was further strengthened relative to those with normal sleep and HRV.

**Conclusions:** To the best of the author's knowledge, this is the first study to suggest a combined effect of poor sleep and low HRV on the odds of metabolic syndrome.

**Key words:** autonomic; heart rate variability; HRV; metabolic syndrome; sleep

## Graphical Abstract



The Role of Sleep and Heart Rate Variability in Metabolic Syndrome:
Evidence from the Midlife in the United States (MIDUS II) Study

N = 966 Participants

↓ **Heart Rate Variability**

**HRV Odds Ratio: 0.59, CI: 0.43-0.79**
❋ Elevated HRV is protective. Those in the upper SDRR quartiles were 1.69 times *less* likely to develop metabolic syndrome

Hyperglycemia

**Metabolic Syndrome**

Obesity

Dyslipidemia

↓ **Sleep Quality**

**Sleep Odds Ratio: 1.6, CI: 1.2-2.1**
❋ Metabolic syndrome was 60% more likely in those with poor sleep quality (Pittsburgh Sleep Quality Index >5)

Hypertension

**Odds Ratio for Combined Effect of Poor Sleep & Low HRV: 2.6, 95% CI: 1.5-4.7**

**Statement of Significance**

The current investigation found that poor sleep and low heart rate variability (HRV) were both associated with metabolic syndrome and that the odds of metabolic syndrome were strongest among those with both poor sleep quality and low HRV. These findings highlight the potential for targeting both HRV and sleep to noninvasively reduce or prevent metabolic syndrome and related chronic diseases.

## Introduction

Metabolic syndrome has become more common over the last 20 years, with a current estimated prevalence of 25%–37% among adults in the general population [1]. Also known as cardiometabolic syndrome, it is characterized by a complex combination of hypertension, abdominal adiposity, impaired glucose tolerance, and dyslipidemia [2]. Each component of metabolic syndrome is a clinically relevant risk factor for multiple chronic disease states, including cardiovascular disease, diabetes and their associated sequelae, and increased mortality risk [3]. The specific pathophysiological processes by which the individual or aggregate components of metabolic syndrome confer an increased risk of adverse health outcomes are still unclear [4]. Developing a better understanding of how modifiable risk factors such as sleep and autonomic activity may influence the metabolic syndrome disease continuum may help to establish more effective disease prevention strategies.

The prevalence of poor sleep, specifically short sleep duration, has increased over time in conjunction with the increased prevalence of metabolic disorders and obesity in the United States [5]. Sleep plays a major role in regulating and optimizing many physiological processes, including metabolic homeostasis [5, 6]. Both subjective and objective (actigraphy, polysomnography) measures have been used to assess sleep pathology, and previous research has shown a modest overlap between the two, although they may also be measuring somewhat different aspects of the sleep/wake cycle [7]. In a meta-analysis evaluating the relationship between sleep duration and metabolic syndrome, the pooled odds ratio (OR) for metabolic syndrome among those with sleep duration <7 h was 1.23 (95% confidence interval [CI]: 1.11 to 1.37) compared to individuals with daily sleep duration of 7–8 h [8]. A dose-response relationship was also observed between reduced sleep duration and increased odds of metabolic syndrome [8]. Cross-sectional studies using self-reported sleep quality measures such as the Pittsburgh Sleep Quality Index (PSQI) have also reported positive associations with metabolic syndrome or its individual components [9–11].

The autonomic nervous system (ANS) plays a critical role in regulating cardiovascular and metabolic function as well as sleep physiology. Sympathetic nervous system (SNS) activity is elevated during the stress response and mobilizes the body for action, for example, by increasing heart rate and blood pressure, releasing energy reserves, and inhibiting the gastrointestinal tract [12, 13]. Parasympathetic activity, mediated by the vagus nerve, generally opposes sympathetic activity. Heart rate variability (HRV) refers to the variation in heart rate over time and is considered an objective measure of both sympathetic and parasympathetic ANS activity [13–15]. Heart rate is influenced by the baroreflex, which maintains blood pressure homeostasis [16, 17]. A stronger baroreflex results in more efficient blood pressure maintenance and higher HRV [16, 17]. Analyses of HRV commonly utilize time and frequency domain indices [15, 18]. Time-domain indices quantify the amount of HRV observed over the course of the monitoring period, whereas frequency-domain measures characterize

repetitive physiological processes such as the respiratory cycle. Both time and frequency domain HRV measures quantify the complex and dynamic interplay between the SNS and the parasympathetic nervous system (PNS). Time-domain HRV measures include the standard deviation of all NN or RR intervals (SDNN or SDRR) and the square root of the mean squared difference of successive RR intervals (RMSSD) to quantify the variability in measurements of interbeat intervals [15]. Low-frequency HRV (LF-HRV) increases in response to both the PNS and SNS activity, whereas high-frequency HRV (HF-HRV) increases in response to PNS activation [15]. SDNN and SDRR reflect both SNS and PNS activity and tend to correlate with LF-HRV depending on measurement conditions. RMSSD is well-correlated with HF-HRV and PNS activity [15].

Elevated HRV is associated with a greater capacity to regulate stress and emotions [19–21], whereas low HRV is maladaptive and has been associated with cardiac complications, psychological and neurological disorders, and increased mortality, particularly among those with underlying chronic disease [21–28]. The ANS regulates major metabolic processes including blood pressure and the disposition of blood glucose and lipids, as well as the secretion of immune and endocrine mediators that influence these processes. Reduced HRV has been associated with adverse changes in several metabolic syndrome components, including waist circumference, triglycerides, high-density lipoprotein (HDL), blood pressure, and serum glucose [29–31]; however, activation of the SNS and suppression of the PNS are not part of the diagnostic criteria [32–35]. HRV indices were lower in individuals with multiple components of metabolic syndrome, and HRV decreased as the number of individual metabolic components achieving criterion values increased [36]. Korean adults with metabolic syndrome had lower mean HRV measures, and all metabolic syndrome components were negatively correlated with HRV [24, 33, 37]. Interventions targeting the ANS are under investigation to address metabolic syndrome components, including hypertension and diabetes [38, 39]. Sleep disturbances have been associated with autonomic irregularities [40–46]. Alternatively, the restorative properties of sleep are thought to be related to the parasympathetic dominance that occurs during non-rapid eye movement sleep [47–49].

Autonomic activity and sleep are both essential physiological processes that influence metabolic function, and both respond to physiological and psychological stressors. Primary ANS functions are to maintain homeostasis and facilitate stress adaptation, whereas sleep facilitates homeostasis but also reflects circadian timing. Metabolic processes are strongly influenced by endogenous circadian timing, and poor sleep can signify circadian rhythm disruption in some circumstances [50]. To the best of the author's knowledge, no studies have examined the combined role of these risk factors in relation to metabolic syndrome. This study tested the hypothesis that metabolic syndrome is associated with poor sleep and reduced HRV, both individually and in combination, in a nationally representative sample of US Adults from the Midlife Development in the United States (MIDUS) study [51].

## Methods
### Study population and procedures
Data from the (MIDUS) II survey and biomarker projects were downloaded from the Inter-University Consortium for Political and Social Research online repository [51, 52]. MIDUS II (2006–2008) is a follow-up of the first MIDUS participants (1995–1996)

that prospectively examined the role of behavioral, psychological, and social factors in age-associated physical and mental health outcomes. The MIDUS II biomarker project assessed a subsample of 1255 participants to ascertain biopsychosocial pathways that contribute to physical and psychological health outcomes, including metabolic syndrome. Participants of the MIDUS II biomarker project were recruited from the original MIDUS study and traveled to one of three General Clinical Research Centers (CRCs) for a clinical assessment. Members of the Milwaukee sample of African Americans and the twin study were also recruited. For this analysis, data from 966 participants with complete measures of HRV, metabolic syndrome components, and PSQI-derived sleep metrics were utilized. Data were collected during a 24-hour stay at one of the three clinics using a standardized protocol that included fasting blood samples, 12 h urine sample collection, a detailed medical history, physical examination, and questionnaires, as described previously [51]. Participants gave their written informed consent, and each MIDUS research center obtained institutional review board approval.

### Measures
#### *Metabolic syndrome.*
The biomarkers included in this analysis targeted the ANS, hypothalamic-pituitary-adrenal axis function, and processes that characterize metabolic syndrome [51]. The presence of metabolic syndrome was ascertained according to criteria established by the National Cholesterol Education Program III (ATP III) [2]. Participants were classified as having metabolic syndrome if they met at least three of the following criteria: waist circumference > 102 cm for men and >88 cm for women; triglycerides ≥ 150 mg/dL, HDL cholesterol < 40 mg/dL for men and <50 mg/dL for women; blood pressure ≥ 130/85 mmHg; or serum glucose ≥ 110 mg/dL.

#### *Sleep.*
Sleep was assessed using the PSQI, which consists of 19 self or bed-partner-rated questions that are used to characterize sleep: quality, onset latency, duration, efficiency, medication use, disturbance, and daytime dysfunction [53]. Each individual sleep component ranges from 0 to 3, and the global sleep score used in the primary analysis is a composite of seven components with scores ranging from 0 to 21, with increasing values indicating poorer sleep quality. A global score >5 was used as the cutoff for poor overall sleep [53, 54].

#### *HRV.*
Following an overnight stay at one of the CRCs, a breakfast meal that included abstinence from caffeine consumption was provided, and a standardized clinical assessment that included HRV electrophysiology was implemented using a previously described protocol [51, 55]. Electrocardiogram (ECG) electrodes were placed on the left and right shoulder and the lower-left quadrant. A respiration band was placed around the chest, and a Finometer beat-to-beat blood pressure cuff was placed around the middle finger of the participant's nondominant hand. While participants were in a seated position, data were recorded during an 11-minute baseline assessment, and those data were used for this analysis. ECG data were digitized at a sampling rate of 500 Hz by a 16-bit National Instruments analog to the digital board (National Instruments, Austin, TX), and custom proprietary software was then used to identify R waves. Research staff visually inspected all ECG waveforms for artifacts. Time-domain indices used in the analysis included the SDRR and RMSSD. Frequency

domain indices used in the analysis included the high (HF-HRV; 0.15–0.50 Hz) and low (LF-HRV; 0.04–0.15 Hz) spectral power frequency bands, which were calculated using interval methods for fast Fourier transformation [56]. The mean value of the HF-HRV and LF-HRV was computed from two 300-second epochs. HF-HRV and LF-HRV values were natural-log transformed (ln) prior to analysis [15].

### Covariates.

Covariates including age, sex, education, race, marital status (single/never married, married or living with a partner, and widowed/divorced), general health, and smoking status were obtained from self-report questionnaires. Regular exercise and certain comorbid conditions (heart disease, diabetes, and depression) were included as they are known to influence cardiometabolic factors, sleep, and HRV [15, 57–59]. Other covariates included medications known to influence HRV, sleep, or metabolic factors, including cholesterol-lowering agents and medications that may increase (cholinergic agents and **β**-adrenergic blocking agents) or decrease (barbiturates, benzodiazepines, antidepressants, antipsychotics, and phenothiazines) PNS activity [59].

### Data analysis

Analyses were performed using SAS version 9.4 (Cary, NC). The characteristics of those with and without metabolic syndrome were compared using chi-square tests for categorical variables and *t*-tests or Wilcoxon rank-sum tests for continuous variables depending on whether or not the normality assumption was met, respectively. These bivariate analyses identified candidate confounders for subsequent analyses ($p ≤ .20$). Candidate confounders were included in the final adjusted general linear or logistic regression models if the variable changed the beta coefficient of the variable of interest by ≥10% or if it was a statistically significant predictor of the outcome ($p ≤ .05$). Linear regression assumptions were evaluated by examining the final model's residuals;, and no violations were observed.

Data analyses initially examined the relationship between global PSQI scores, HRV indices, and individual components of metabolic syndrome (dependent variables) using Spearman correlations. These analyses were performed among all participants and then repeated with stratification among those with and without metabolic syndrome and further stratified by the presence of three, four, and five metabolic syndrome components. Multivariable logistic regression was then used to estimate the independent association between poor sleep using the global PSQI score and its individual components (quality, onset latency, duration, efficiency, medication use, disturbance, and daytime dysfunction) or low HRV on metabolic syndrome by calculating the OR and CI. The independent variables of interest for this analysis included the PSQI score as a continuous or categorical variable (global PSQI sleep score >5 vs ≤ 5) and log-transformed continuous values of each HRV variable (ln LF-HRV, ln HF-HRV, ln SDRR, and ln RMSSD). In exploratory analyses, individual components of the PSQI were examined separately.

To evaluate the individual and combined effect of poor sleep and reduced HRV on the odds of metabolic syndrome, separate multivariable logistic regression models were fit using global PSQI sleep score as a continuous or categorical variable, a single HRV measure of interest (ln LF-HRV, ln HF-HRV, ln SDRR, and ln RMSSD), and the interaction term between the individual sleep and HRV measures. Separate models were used to examine the potential interaction between the global PSQI score and each HRV measure in relation to the odds of metabolic syndrome. Interaction terms with *p*-values ≤ .20 were selected for subsequent stratified analyses. Participants were separated into groups with low (first HRV quartile) and high HRV (quartiles 2–4), and the association between global PSQI score (independent variable) or individual PSQI components (independent variable) and metabolic syndrome (dependent variable) was assessed within each stratum. In supplemental analyses, general linear regression models were used to compute adjusted (least-squares or LS) means of each HRV measure among the participants with good and poor sleep (global PSQI sleep score > 5) and among participants stratified by metabolic syndrome.

Finally, Spearman correlations or adjusted general linear regression models were used to examine the relationship between PSQI scores, HRV indices, and individual components of metabolic syndrome (dependent variables) as supplementary analyses.

## Results

### Demographic characteristics

Among the 1255 MIDUS II biomarker project participants, 966 had complete PSQI, metabolic syndrome, and HRV data. The study population was primarily female (55%) and married (66%), with a mean age (±SD) of 54 ± 11 years (Table 1). Metabolic syndrome was present in 36% of the study sample, and participants with and without metabolic syndrome did not differ by age, marital status, cancer history, or depression (Table 1). Participants with metabolic syndrome had greater waist circumference, less physical activity, and were more likely to have diabetes and to take medications for cholesterol management or sex-hormone replacement, or medications that affect ANS activity (Table 1). Among participants with metabolic syndrome, a majority (60%) met the minimum criteria for metabolic syndrome (three components). The mean number of metabolic components for all participants and those with or without metabolic syndrome was 2.0 ± 1.4, 3.5 ± 0.7, and 1.2 ± 0.8, respectively.

### Relationship between global PSQI score, HRV, and individual metabolic syndrome components

Correlation coefficients between global PSQI score and HRV or individual metabolic syndrome measures (waist circumference, systolic and diastolic blood pressure, HDL, and triglycerides) are presented in Supplementary Table S1. Global PSQI scores were negatively correlated with ln LF-HRV among participants with and without metabolic syndrome, and no other HRV indices were correlated with global PSQI scores. When stratified by metabolic syndrome severity, global PSQI scores were negatively correlated with ln LF-HRV, ln SDRR, and ln RMSSD among participants with three metabolic syndrome components. However, no statistically significant relationships were observed among the participants with four or five metabolic syndrome components. Triglycerides were positively correlated with global PSQI scores among those with metabolic syndrome, and no other statistically significant correlations were noted.

### Association between poor sleep or low HRV and metabolic syndrome

When analyzing the global PSQI score as a continuous variable, the odds of meeting the criteria for metabolic syndrome increased by 7% for every one-unit increase (Table 2). Participants who were classified as poor sleepers (global PSQI sleep score >5) had 58% increased odds of meeting the criteria for metabolic syndrome

**Table 1.** Demographic characteristics with stratification by the presence of metabolic syndrome, MIDUS II study, 2004–2009 (n = 966)

| Characteristics | Overall (n = 966) | Without metabolic syndrome* (n = 622) | With metabolic syndrome (n = 344) | P† |
|---|---|---|---|---|
| | Mean ± SD or n (%) | | | |
| Age (years) | 54.0 ± 11.6 | 53.7 ± 11.9 | 54.5 ± 10.9 | .35 |
| Body mass index (kg/m²) | 29.7 ± 6.6 | 27.5 ± 5.6 | 33.8 ± 6.3 | <.01 |
| Waist circumference (cm) | 97.3 ± 16.2 | 91.5 ± 14.3 | 108.0 ± 13.7 | <.01 |
| Metabolic syndrome components | | | | |
| Three | — | — | 205 (60) | — |
| Four | | | 96 (28) | |
| Five | | | 43 (13) | |
| Sex | | | | |
| Male | 421 (44) | 268 (43) | 153 (45) | .68 |
| Female | 545 (56) | 354 (57) | 191 (56) | |
| Marital status | | | | |
| Single | 99 (10) | 62 (10) | 37 (11) | .28 |
| Married | 640 (66) | 423 (68) | 217 (63) | |
| Divorced/widowed/separated | 227 (24) | 137 (22) | 90 (26) | |
| Current smoker | | | | |
| Yes | 139 (14) | 83 (13) | 56 (16) | .22 |
| No | 826 (86) | 538 (87) | 288 (84) | |
| Regular physical activity at least three times/week | | | | |
| Yes | 749 (76) | 511 (82) | 238 (69) | <.01 |
| No | 217 (24) | 111 (18) | 106 (31) | |
| Hypertension | | | | |
| Yes | 324 (34) | 155 (25) | 169 (49) | <.01 |
| No | 642 (67) | 467 (75) | 175 (51) | |
| Cancer | | | | |
| Yes | 125 (13) | 75 (12) | 50 (15) | .27 |
| No | 841 (87) | 547 (88) | 294 (86) | |
| Diabetes | | | | |
| Yes | 109 (11) | 31 (5) | 78 (23) | <.01 |
| No | 857 (89) | 591 (95) | 266 (77) | |
| Depression | | | | |
| Yes | 179 (19) | 108 (17) | 71 (21) | .21 |
| No | 787 (82) | 514 (83) | 273 (79) | |
| Cholesterol medication | | | | |
| Yes | 265 (27) | 138 (22) | 127 (37) | <.01 |
| No | 701 (73) | 484 (75) | 217 (63) | |
| Sex-hormone medication | | | | |
| Yes | 108 (11) | 79 (13) | 29 (8) | .04 |
| No | 858 (89) | 543 (87) | 315 (92) | |
| Medications that increase PNS activity | | | | |
| Yes | 138 (14) | 67 (11) | 71 (21) | <.01 |
| No | 828 (86) | 555 (89) | 273 (79) | |
| Medications that decrease PNS activity | | | | |
| Yes | 178 (18) | 103 (17) | 75 (22) | .04 |
| No | 788 (82) | 519 (83) | 269 (78) | |

*Metabolic syndrome is defined according to the National Cholesterol Education Program Expert Panel criteria [2].
†Calculated with independent sample t-tests or Wilcoxon rank-sum test (for continuous variables with normal and skewed distributions, respectively), and chi-square tests (for categorical variables) for participants with and without metabolic syndrome.
SD, standard deviation; PNS, parasympathetic nervous system.

**Table 2.** Association between global PSQI sleep score, HRV, and metabolic syndrome[*], MIDUS II study, 2004–2009 (*n* = 966)

| Measures | Metabolic syndrome | | | |
|---|---|---|---|---|
| | Crude OR (95% CI) | *P* | Adjusted OR (95% CI) | *P* |
| PSQI sleep measures | | | | |
| Global score (continuous)[†] | 1.07 (1.03 to 1.11) | <.01 | 1.07 (1.03 to 1.11) | <.01 |
| Global score (categorical)[‡] | | | | |
| Good (≤5) | Reference | | Reference | |
| Poor (>5) | 1.62 (1.24 to 2.11) | <.01 | 1.58 (1.19 to 2.10) | <.01 |
| HRV | | | | |
| ln (HF-HRV ms$^2$)[§] | 0.89 (0.81 to 0.99) | .03 | 0.89 (0.80 to 0.99) | .04 |
| ln (LF-HRV ms$^2$)[‖] | 0.80 (0.71 to 0.89) | <.01 | 0.82 (0.72 to 0.92) | <.01 |
| ln (SDRR ms)[¶] | 0.57 (0.43 to 0.76) | <.01 | 0.59 (0.43 to 0.79) | <.01 |
| ln (RMSSD ms)[#] | 0.77 (0.62 to 0.95) | .01 | 0.75 (0.60 to 0.94) | .01 |

ORs for having metabolic syndrome are based on a one-unit change in HRV or continuous PSQI-derived sleep measures. Higher global PSQI sleep scores indicate poorer overall sleep with a range of 0–21 (good: ≤5, poor: >5) [53].
CI, confidence interval; HF-HRV, high frequency heart rate variability; LF-HRV, low frequency heart rate variability; SDRR, standard deviation of RR intervals; RMSSD, root mean square of successive differences; ms, milliseconds; ln, natural logarithm; PNS, parasympathetic nervous system; PSQI, Pittsburgh sleep quality index; OR, odds ratio.
[*]Metabolic syndrome is defined according to the National Cholesterol Education Program Expert Panel criteria [2].
[†]Adjusted for age, cholesterol medication, depression, sex, and medications that increase PNS activity (cholinergic agents and β-adrenergic blocking agents), and medications that decrease PNS activity (barbiturates, benzodiazepines, antidepressants, antipsychotics, and phenothiazines).
[‡]Adjusted for age, cholesterol medication, smoking, depression, sex, medications that increase PNS activity, and medications that decrease PNS activity.
[§]Adjusted for age, cholesterol medication, smoking, sex, and medications that increase PNS activity.
[‖]Adjusted for age, cholesterol medication, smoking, sex, and medications that increase PNS activity.
[¶]Adjusted for age, cholesterol medication, sex, and medications that increase PNS activity.
[#]Adjusted for age, cholesterol medication, smoking, sex, and medications that increase PNS activity.

(Table 2) versus referents. Each of the PSQI components (continuous variables) had a statistically significant positive association with metabolic syndrome, with the exception of sleep efficiency and sleep medication use, after adjustment for confounding (Supplementary Table S5). Finally, a one-unit increase in each HRV measure (HF-HRV, LF-HRV, SDRR, or RMSSD) was associated with decreased odds of metabolic syndrome (Table 2).

## Combined association of poor sleep and low HRV with metabolic syndrome

When the relationship between global PSQI score and metabolic syndrome was stratified by HRV status, the results were mixed depending on the HRV measure that was evaluated. For LF-HRV (≤103 ms$^2$) and SDRR (≤23 ms), an association between global PSQI score and metabolic syndrome was only observed among those with low HRV levels (Table 3). However, when participants were stratified based on HF-HRV or RMSSD, the relationship between global PSQI score and metabolic syndrome was similar in both strata (Table 3). The greatest odds of metabolic syndrome tended to occur among the participants with both low HRV and poor sleep quality (global PSQI scores > 5). Among the individual PSQI sleep components, poor sleep quality, latency, duration, sleep disturbance, and daytime dysfunction tended to be most strongly associated with metabolic syndrome within strata of low LF-HRV or SDRR (Supplementary Table S6).

In supplementary analyses, participants with metabolic syndrome had an inverse relationship between global PSQI score and ln LF-HRV after adjustment for confounding factors (Supplementary Table S2). However, there was no relationship between the global PSQI score and any of the HRV measures among participants without metabolic syndrome or in the entire sample combined (Supplementary Table S2). There were modest differences in mean adjusted global PSQI scores between those with and without metabolic syndrome (Supplementary Table S3).

Participants without metabolic syndrome had higher adjusted mean HRV estimates compared to those with metabolic syndrome (Supplementary Table S3). Among all participants, there were no notable differences in adjusted mean HRV measures between those with and without poor sleep (Supplementary Table S4). Among participants with metabolic syndrome, those with good sleep had higher mean values of ln LF-HRV relative to those with poor sleep. There were no other statistically significant differences among the other LS mean HRV estimates (Supplementary Table S4).

## Discussion

In this population-based sample of middle-aged, older adults in the United States, poor sleep and reduced HRV were both individually associated with metabolic syndrome after controlling for relevant covariates. Participants with global PSQI score >5 had ~58% increased odds of meeting the metabolic syndrome criteria compared to participants with better sleep profiles, and a one-unit increase in ln (HRV) values were associated with a ~11%–41% decreased odds of metabolic syndrome. When the PSQI subscales were examined, poor sleep quality, shorter sleep duration, longer sleep latency, sleep disturbance, and daytime dysfunction each exhibited independent associations with metabolic syndrome. It was unclear whether changes in certain metabolic components may be more influential in driving these associations, although correlations were strongest between global PSQI scores and triglycerides both in the total sample and among those with metabolic syndrome. To the best of the authors' knowledge, this study was the first to examine the combined effects of HRV and poor sleep on metabolic syndrome. A relationship between poor sleep and low HRV (primarily LF-HRV or SDRR) was observed among those with metabolic syndrome but not among those without this condition (Supplementary Tables S1 and S2). Furthermore, those

**Table 3.** Association between global PSQI sleep score[*] and metabolic syndrome[†], stratified by HRV indices, MIDUS II study, 2004–2009 (*n* = 966)

| PSQI sleep measures | Crude OR (95% CI) | | Adjusted OR (95% CI) | |
|---|---|---|---|---|
| | HF-HRV | | HF-HRV | |
| | Low | High | Low | High |
| Global sleep score (Continuous)[‡] | 1.07 (1.00 to 1.15) | 1.06 (1.02 to 1.11) | 1.07 (0.99 to 1.15) | 1.07 (1.02 to 1.11) |
| Global sleep score (Categorical)[§] | | | | |
| Good (≤5) | Reference | Reference | Reference | Reference |
| Poor (>5) | 1.85 (1.11 to 3.09) | 1.51 (1.10 to 2.07) | 1.74 (1.00 to 3.04) | 1.49 (1.07 to 2.09) |
| | LF-HRV | | LF-HRV | |
| | Low | High | Low | High |
| Global sleep score (continuous) [‡] | 1.12 (1.05 to 1.20) | 1.04 (1.00 to 1.08) | 1.12 (1.04 to 1.20) | 1.04 (0.99 to 1.09) |
| Global sleep score (categorical)[§] | | | | |
| Good (≤5) | Reference | Reference | Reference | Reference |
| Poor (>5) | 2.40 (1.43 to 4.01) | 1.34 (0.98 to 1.84) | 2.09 (1.20 to 3.65) | 1.38 (0.98 to 1.93) |
| | SDRR | | SDRR | |
| | Low | High | Low | High |
| Global sleep score (continuous)[‡] | 1.15 (1.07 to 1.24) | 1.04 (0.99 to 1.08) | 1.15 (1.07 to 1.24) | 1.04 (0.99 to 1.08) |
| Global sleep score (categorical)[§] | | | | |
| Good (≤5) | Reference | Reference | Reference | Reference |
| Poor (>5) | 2.79 (1.65 to 4.72) | 1.31 (0.96 to 1.79) | 2.63 (1.48 to 4.68) | 1.31 (0.94 to 1.82) |
| | RMSSD | | RMSSD | |
| | Low | High | Low | High |
| Global sleep score (continuous)[‡] | 1.10 (1.02 to 1.17) | 1.06 (1.01 to 1.10) | 1.10 (1.02 to 1.18) | 1.05 (1.01 to 1.10) |
| Global sleep score (categorical)[§] | | | | |
| Good (≤5) | Reference | Reference | Reference | Reference |
| Poor (>5) | 2.00 (1.19 to 3.34) | 1.49 (1.09 to 2.03) | 1.84 (1.05 to 3.23) | 1.47 (1.05 to 2.05) |

ORs for having metabolic syndrome are based on a one-unit change in continuous sleep score. For this analysis, participants in the lowest quartile are considered to have reduced HRV (Low HF-HRV: ≤56 ms$^2$; Low LF-HRV: ≤103 ms$^2$; Low SDRR: ≤23 ms; Low RMSSD: ≤103 ms); whereas the remaining three quartiles are considered to have nonreduced or normal HRV (High HF-HRV: >56 ms$^2$; High LF-HRV: >103 ms$^2$; High SDRR: >23 ms; High RMSSD: >103 ms). Interaction term *p*-values between global sleep score and individual HRV (HF-HRV, LF-HRV, SDRR, and RMSSD) indices were (.03, <.01, <.01, and <.01, respectively).
CI, confidence interval; HF-HRV, high frequency heart rate variability; LF-HRV, low frequency heart rate variability; SDRR, standard deviation of RR intervals; RMSSD, root mean square of successive differences; ms, milliseconds; PNS, parasympathetic nervous system; PSQI, Pittsburgh sleep quality index; OR, odds ratio.
[*]Higher global PSQI sleep scores indicate poorer sleep quality with a range of 0–21 [53].
[†]Metabolic syndrome is defined according to the National Cholesterol Education Program Expert Panel criteria [2].
[‡]Adjusted for cholesterol medication, sex, and medications that increase (cholinergic agents and β-adrenergic blocking agents) and decrease (barbiturates, benzodiazepines, antidepressants, antipsychotics, and phenothiazines) PNS activity.
[§]Adjusted for cholesterol medication, depression, smoking, sex, and medications that increase and decrease PNS activity.

with both reduced HRV (LF-HRV, SDRR) and poor self-reported sleep (particularly those with global PSQI scores > 5, poor sleep quality, shorter sleep duration, and daytime dysfunction) were approximately two times as likely to have metabolic syndrome compared to those with only one of these risk factors, and the results persisted after adjustment for confounding.

The results related to poor sleep quality are consistent with previous studies that have examined self-reported sleep using global PSQI and its individual components in relation to metabolic syndrome [32, 60]. For example, a population-based study of Japanese citizens (*N* = 1481) reported elevated odds of poor sleep among those with metabolic syndrome (females OR: 2.37; 95% CI: 1.23 to 4.58; males OR: 2.71; 95% CI: 1.45 to 5.07) [10]. In another study among participants from the University of Pittsburgh's Adult and Human Behavior Project, poor sleep quality was associated with metabolic syndrome in a population of middle-aged US adults [9]. However, an analysis of multi-ethnic, midlife women from the SWAN Sleep Study found no difference in global PSQI sleep scores between participants with and without metabolic

syndrome [61], and a 2012 study among African Americans did not find an association between sleep quality and metabolic syndrome or its components [62]. Discrepancies among these studies may be due to inherent differences in the populations studied or heterogeneity of the study designs or analyses that were performed. For example, the samples used in the Hall *et al.* and the Kazman *et al.* studies [61, 62] consisted of women only, whereas the Jennings *et al.* study [9] was predominantly male. Furthermore, the mean PSQI global scores for the male dominant (4.6 ± 2.6) samples were lower than female samples (6.6 ± 3.8 and 6.2 ± 2.3, respectively) [9, 61, 62].

The current analysis was also consistent with previous studies that reported greater odds of metabolic syndrome among those with reduced time (RMSSD, SDRR) or frequency (LF-HRV, HF-HRV) domain HRV measures. A 2010 cross-sectional study utilizing data from the PROgnostic indicator OF cardiovascular and cerebrovascular events (PROOF) cohort study found lower LF-HRV in those with metabolic syndrome using short-term HRV recordings; and no differences in HF-HRV [35]. A prospective study examining

early-stage cardiac autonomic dysfunction found that participants with metabolic syndrome had reduced HRV indices (SDNN, LF-HRV, and HF-HRV) relative to healthy controls [32]. Another study that examined autonomic activity in a population at risk for metabolic syndrome reported decreased SDNN and HF-HRV with an increasing number of metabolic syndrome components (≥3) [63]. The Twins Heart Study investigated psychological and biological risk factors for cardiovascular disease and reported that reduced HRV was associated with metabolic syndrome after controlling for relevant covariates and genetic factors [64]. A case-control study consisting of middle-aged and older working men found that participants with metabolic syndrome had lower HRV levels compared to healthy controls [65]. The accumulation of metabolic syndrome components may be due in part to the chronic overactivation of the SNS and subsequent disruption of ANS homeostasis, which may contribute to the dysregulation of metabolic processes [63, 66]. The ANS plays a vital role in regulating metabolic processes, but it is unclear whether ANS dysfunction precedes the development of metabolic syndrome, although some evidence supports this possibility [24, 37].

Results from the current analysis indicate that the greatest odds of metabolic syndrome occurred among those with both poor sleep quality and reduced HRV (primarily LF-HRV and SDRR). This suggests that ANS dysfunction and poor sleep are more strongly coupled during metabolic syndrome, although studies focusing on the temporal sequence between these processes and the development of metabolic syndrome would be needed to fully elucidate such inter-relationships. There is significant bidirectional crosstalk between the ANS and cardiovascular systems during sleep, and both systems influence metabolic activity. During non-rapid eye movement (NREM) sleep, autonomic modulation driven by vagal PNS activity reduces heart rate and blood pressure, whereas REM sleep is primarily under sympathetic control [67]. In a cross-sectional study of college-aged participants, a negative association was observed between self-reported sleep latency and LF-HRV ($r = -0.262$, $p = .002$) or SDNN ($r = -0.137$, $p = .04$), although no other relationships were observed between sleep quality and HRV indices [44]. In another study, increased LF-HRV and decreased HF-HRV were observed in objectively defined insomniacs compared to healthy controls during all sleep stages [40]. In a cross-sectional analysis of actigraphy-based measures, short sleep duration, low sleep efficiency, and insomnia were each associated with lower parasympathetic tone and SNS activation [41]. Multiple studies have reported that poor sleep disrupts the ability of the PNS to modulate sympathetic activity [68–70]. In the Penn State Adult Cohort study, mortality risk associated with metabolic syndrome was twofold greater among those with short sleep duration, and those with short sleep had greater central autonomic and metabolic dysfunction relative to normal sleepers [71]. The authors speculate that chronic sleep disturbances may lead to persistent SNS hyperactivation culminating in the exhaustion of the stress response and loss of autonomic and metabolic homeostasis [44]. The low LF-HRV values that were associated with increased odds of metabolic syndrome in the present study are consistent with this possibility. Reduced LF-HRV has been associated with burnout and exhaustion in workers, and low RMSSD is associated with exhaustion from burnout and depression both under experimental conditions [72–74] and at rest [75]. The role of circadian rhythms in regulating metabolic processes has been established [50, 76], and poor sleep may be an indicator of circadian disturbances. While circadian rhythms were not directly measured or evaluated in the current study, associations between metabolic syndrome and shorter sleep duration, daytime dysfunction, and sleep disturbance may suggest a potential role for this pathway. Based on the above evidence, the authors have conceptualized the following theoretical model; sleep disruption may elicit both stress and metabolic desynchronization, which combined with other chronic metabolic (inactivity, overeating, other poor lifestyle choices and behaviors) and potential psychological stressors (anxiety, low self-esteem, depression) can lead to ANS disruption, dysregulation, and pathological changes in metabolic homeostasis that eventually manifest as metabolic syndrome.

This study had several noteworthy strengths and limitations. Limitations include a relatively homogeneous sample (~92% white and ~42% with a college degree or more). Another limitation was that objective sleep measures were not used in the analysis, although the PSQI has been extensively validated, including in a subset of MIDUS study participants [77]. Additionally, this study was not able to evaluate the potential role of obstructive sleep apnea (OSA) or sleep-disordered breathing on the development of the metabolic syndrome. Previous studies have reported an association between OSA and metabolic syndrome or some of its components [78, 79], likely due to repetitive oxygen desaturation leading to beta cell disruption and subsequent insulin resistance, SNS excitation, and the production of inflammation mediators [79]. Another limitation is that the study utilized short-term HRV recordings in the sitting position. While the results were consistent with previous studies utilizing short-term, nighttime, and 24 h HRV recordings, both the nighttime and 24 h measures tended to have stronger associations with metabolic syndrome [35]. This may suggest a role for sleep or circadian rhythm disturbances as a potential contributor to ANS dysregulation and disrupted metabolic homeostasis and is consistent with results from the current study. Long-term, 24 h or overnight recordings may contribute to a more comprehensive evaluation of various metabolic processes potentially including their circadian components [50]. For example, a 2010 study examined the relationship between ANS activity and metabolic syndrome and reported negative associations between LF-HRV and metabolic syndrome using 24 h HRV recordings that were not apparent using short-term recordings [35]. Posture used for HRV data collection is also a potential limitation; however, the literature is mixed regarding optimal positioning, and all participants in this study were measured using the same standardized procedure [80, 81]. It is possible that some of the participants did not meet the National Cholesterol Education Program III criteria for metabolic syndrome because they were taking medications based on their risk profile for cardiovascular disease. For example, some participants may have been misclassified as not having metabolic syndrome because they were taking lipid-lower agents. However, the analyses were adjusted for use of cholesterol-lowering agents and other key medications when it was appropriate based on the variable selection criteria. Finally, participants were required to travel to one of three research centers, which may have introduced selection bias and reduced generalizability [51, 82]. Strengths of this study include the robust sample size, clinical, and psychosocial assessments that were performed using validated measures and standardized protocols, and analyses that adjusted for many relevant covariates. One innovation was the evaluation of the potential impacts of both poor sleep and low HRV on metabolic syndrome. Due to the study's cross-sectional design, it was not possible to elucidate the complex temporal relationships between sleep and HRV or their subsequent association with metabolic syndrome, and it

was therefore not possible to make causal inferences regarding the results.

In conclusion, the current investigation found that poor sleep and low HRV were both associated with metabolic syndrome and that the odds of metabolic syndrome were strongest among those with both poor sleep quality and low HRV (LF-HRV, SDRR). These findings highlight the potential for targeting both HRV and sleep to noninvasively reduce or prevent cardiometabolic and related chronic diseases.

## Supplementary Material

Supplementary material is available at *SLEEP* online.

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## Author Contributions

TLN and JBB devised the main conceptual ideas and design for the analysis. TLN performed the analysis, and JBB, MDW, JPG, and ACM assisted with the evaluation and interpretation of the results and supervision of the work. TLN and JBB prepared the initial manuscript. JBB, MDW, JPG, and ACM provided critical feedback and conducted an internal scientific peer review of the manuscript. All authors discussed the results and concurred that the manuscript is suitable for submission for publication.

## Disclaimer

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