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Original Article

ORIGINAL ARTICLE

The association between rest-activity rhythms and glycemic markers: the US National Health and Nutrition Examination Survey, 2011–2014

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Abstract

Objectives: Previous studies conducted in mostly homogeneous sociodemographic samples have reported a relationship between weakened and/or disrupted rest-activity patterns and metabolic dysfunction. This study aims to examine rest-activity rhythm characteristics in relation to glycemic markers in a large nationally representative and diverse sample of American adults.

Methods: This study used data from the National Health and Nutrition Examination Survey 2011–2014. Rest-activity characteristics were derived from extended cosine models using 24-hour actigraphy. We used multinomial logistic regression and multiple linear regression models to assess the associations with multiple glycemic markers (i.e., glycated hemoglobin, fasting glucose and insulin, homeostatic model assessment of insulin resistance, and results from the oral glucose tolerance test), and compared the results across different categories of age, gender, race/ethnicity, and body mass index.

Results: We found that compared to those in the highest quintile of F statistic, a model-fitness measure with higher values indicating a stronger cosine-like pattern of daily activity, participants in the lowest quintile (i.e, those with the weakest rhythmicity) were 2.37 times more likely to be diabetic ($OR_{Q1\ vs.\ Q5}$ 2.37 (95% CI 1.72, 3.26), *p*-trend < .0001). Similar patterns were observed for other rest-activity characteristics, including lower amplitude (2.44 (1.60, 3.72)), mesor (1.39 (1.01, 1.91)), and amplitude:mesor ratio (2.09 (1.46, 2.99)), and delayed acrophase (1.46 (1.07, 2.00)). Results were consistent for multiple glycemic biomarkers, and across different sociodemographic and BMI groups.

Conclusions: Our findings support an association between weakened and/or disrupted rest-activity rhythms and impaired glycemic control among a diverse US population.

Statement of Significance

Weakened rest-activity patterns have been linked to metabolic dysfunction. However, all previous studies focused on older adults who were predominantly white, and it is unclear how findings from these studies can be generalized to other populations. In a nationally representative sample of noninstitutionalized US adults, we found that diabetes and impaired glycemic control were more prevalent among participants with weaker rest-activity rhythms. We found these associations to be robust across populations with different sociodemographic characteristics and BMI status. Notably, weaker rest-activity rhythm was associated with diabetes across all racial/ethnic groups. These findings invite further investigation of the role of rest-activity patterns in metabolic health, particularly in populations with diverse sociodemographic characteristics, lifestyle factors, and health status.

Key words: rest-activity rhythm; metabolic health; glycemic markers; diabetes; nationally representative population

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Introduction

Diabetes is a common chronic condition in the adult population and major contributor to cardiovascular diseases (CVD), renal failure, cognitive decline, and mortality. It is estimated that over 10% of the US population have diabetes [1] and the total cost attributable to diabetes was $327 billion in 2017 [2]. The prevalence of diabetes increased substantially across all ages, sex, and racial/ethnic groups in recent decades [3]. There are also considerable disparities in diabetes, with higher prevalence among non-Hispanic blacks, Hispanics, and Asians relative to non-Hispanic whites [4]. Decades of research has identified numerous lifestyle risk factors for diabetes, particularly unhealthy eating and physical inactivity. More recently, circadian disruption has emerged as a novel risk factor for diabetes [5].

The rest-activity rhythm consists of sleep, physical activity and sedentary behaviors that occur during a 24-hour period. It is a central behavioral manifestation of the internal circadian rhythm that plays an important role in the entrainment of circadian clocks in metabolic tissues such as skeletal muscle [6]. Thus, there is a bidirectional relationship between circadian disruption and weakened and/or disrupted rest-activity patterns [6]. Given the bidirectional relationship, efforts to understand how intervening upon rest-activity rhythm to improve metabolic health have gained traction [7]. Several previous studies have linked rest-activity patterns measured by 24-hour actigraphy with metabolic dysfunction (e.g., higher body mass index (BMI), metabolic syndrome, dyslipidemia, and diabetes) in adult populations [8–10]. We recently found that multiple rest-activity parameters, including a lower amplitude and less robust overall rhythmicity, were associated with higher prevalence and incidence of diabetes in older men [10]. However, the evidence linking rest-activity rhythm characteristics and diabetes remains limited. Moreover, almost all previous studies focused on older adults who were predominantly white, and it is unclear how findings from these studies can be generalized to other populations. Given existing racial disparities in diabetes in the US [4], it is important to study the association between rest-activity rhythms and diabetes in more diverse populations.

Using the National Health and Nutrition Examination Survey (NHANES) 2011–2014, a nationally survey of the US population that oversampled racial/ethnic minority groups, we investigated the association between characteristics of rest-activity rhythms and multiple glycemic markers, including glycated hemoglobin (HbA1c), fasting glucose and insulin, homeostatic model assessment of insulin resistance (HOMA-IR), and results from the oral glucose tolerance test (OGTT). Because of the large and diverse samples, we were also able to examine the association by different age, gender, race/ethnicity, and BMI groups.

Methods

Study population

This analysis included a nationally representative sample of adults from the NHANES, 2011–2014 [11]. Conducted by the National Center for Health Statistics at the Center for Disease Control and Prevention, the NHANES is a cross-sectional survey to assess the health status of the noninstitutionalized civilian population in the US. Participants were interviewed for sociodemographic information, lifestyle factors, and health status and medical history. Laboratory tests, physiological measures, and biosample collection were performed at a mobile examination center (MEC). The NHANES 2011–2014 represents the first nationally representative sample in the US with 24-hour rest and activity data assessed by wrist actigraphy.

Measurement of rest-activity rhythms

Participants who were three years or older were asked to wear an ActiGraph GT3X+ (Pensacola) on the wrist of the nondominant hand for seven full days (midnight to midnight) to measure 24-hour rest and activity. The device was water-resistant and programmed to obtain triaxial measure of acceleration at 80 Hz sampling intervals. Details of the physical activity monitor protocol were published on the NHANES website [12]. Actigraphy data underwent quality review by contractors at Northeastern University under the supervision of staff and collaborators from the National Cancer Institute and National Center for Health Statistics. Invalid measurements were flagged based on criteria published online [13]. The rest of the data were further categorized into wake wear, sleep wear, or nonwear using an open-source published algorithm [14]. In our analysis, valid data was determined as those categorized as wake and sleep wear. We further defined a valid day of recording as having at least 20 hours of valid data and a participant with valid actigraphy data as having at least 4 valid days.

We used the 5-minute sum of the acceleration measurements obtained on all three axes at the minute level (specified in Monitor-Independent Movement Summary (MIMS) units) to derive rest-activity rhythm parameters using the extended cosine model [15]. By applying an anti-logistic transformation, the model fits activity data to a squared wave form. We derived five parameters as the measures of rest-activity rhythms. Our primary measure of the overall rhythmicity was the F statistic, a model goodness-of-fit measure of the cosine model [15]. Higher values of the F statistic indicate stronger and more robust overall rhythmicity. In addition, we also examined four variables that measured different aspects of the rest-activity rhythm: 1) Amplitude was measured as the difference between the peak and nadir of the fitted curve, and higher values indicated larger rhythm strength. 2) Midline estimating statistic of rhythm, or mesor, was measured as minimum+1/2 amplitude, and higher values indicated a higher average level of activity. 3) Amplitude:mesor ratio was calculated as a normalized measure of rhythm strength accounting for average activity levels. 4) Acrophase was measured as the time of peak activity of the fitted curve, and higher values indicated a later peak. All rest-activity parameters were grouped based on quintiles, with the quintile presumed as having the lowest risk (Q1 for acrophase, and Q5 for all others) as the reference, as was done previously to enable direct comparisons with earlier studies [10].

Measurement of glycemic markers

Our main analysis focused on the diabetic status assessed using HbA1c levels, combined with self-reported information on medical history and medication use. HbA1c was measured from blood samples taken from participants who were 12 or older and visited the MEC. Blood samples were processed, stored, and shipped to the Fairview Medical Center Laboratory at the

University of Minnesota, Minneapolis, Minnesota for analysis. HbA1c was measured by the Tosoh Automated Glycohemoglobin Analyzer HLC-723G8 (South San Francisco, CA, USA). We categorized HbA1c status using previously published criteria [16]: low (<5%), normal (5–5.6%), prediabetic (5.7–6.4%), and diabetic (≥6.5% or self-reported diagnosis of diabetes or use of diabetes medication).

Our secondary analysis focused on fasting glucose, fasting insulin, HOMA-IR, and OGTT results, which were measured in a randomly selected sample of participants 12 or older who visited the morning session at the MEC. Blood glucose concentration was measured by a hexokinase method. Insulin level was determined by enzyme-linked immunosorbent assay. Because of changes in insulin measurement methods from 2011–2012 to 2013–2014, we applied the conversion algorithm as recommended by the NHANES to match the 2013–2014 values to the 2011–2012 values: $Insulin_{2011–2012} = 10^{**}(1.024*\log10(Insulin_{2013–2014}) – 0.0802)$. HOMA-IR was calculated as fasting insulin (mg/dl) x fasting glucose (uIU/ml)/ 405 [17]. OGTT results were based on plasma glucose levels measured two hours after ingesting 75 g glucose orally. For OGTT, there were several additional exclusion criteria including hemophilia and chemotherapy safety exclusions, fasting less than 9 hours, taking insulin or oral medications for diabetes, refusing phlebotomy, and not drinking the entire Trutol glucose solution within the allotted time. All four secondary outcome variables were log-transformed to improve normality. Detailed lab protocols for outcome measurements are published on the NHANES website [18].

Covariates

Study participants reported sociodemographic characteristics (age, gender, race/ethnicity, education, household income, marital status) and lifestyle factors (smoking, alcohol consumption) in interviews. Dietary intake was measured by two 24-h dietary recalls conducted 3–10 days apart. BMI was measured at MEC. Sleep duration and total physical activity (total acceleration measurement value in MIMS units) were derived from the actigraphy data [14].

Analytic sample

Of the 19 931 participants in NHANES 2011–2014, we focused on those age 20 years or older (*N* = 11 329) because this age cutoff was used in a previous study to estimate the prevalence of diabetes in an adult population in the US [4]. Of these, we excluded those who had no measures of rest-activity rhythms (*N* = 2736), had less than 4 days of valid recording (*N* = 1323), or a missing HbA1c measure (*N* = 242). We also excluded pregnant women at the time of the survey (*N* = 59). The final analytic sample focusing on HbA1c included 6975 adults. For the analysis using fasting glucose, fasting insulin, HOMA-IR, and OGTT results as the outcomes, we further excluded those who reported taking medication to lower blood sugar (*N* = 911). Because assays on fasting glucose and insulin, and the OGTT were performed on a subsample of participants, the analyses for these markers focused on those with available outcome variables. The sample sizes were 2938 for fasting glucose, 2836 for fasting insulin, 2834 for HOMA-IR, and 2602 for OGTT. Figure 1 presents a flow chart for deriving the respective analytic samples.

Statistical analysis

NHANES assigns sample weights to allow findings to be generalized to all civilian, noninstitutionalized populations living in the United States. We used the full sample MEC exam weight for analysis on HbA1c, the fasting subsample weight for fasting glucose, fasting insulin, and HOMA-IR, and the OGTT subsample weight for OGTT results. To examine the association between rest-activity rhythm parameters and HbA1c categories, we used multinomial logistic regression where the normal HbA1c

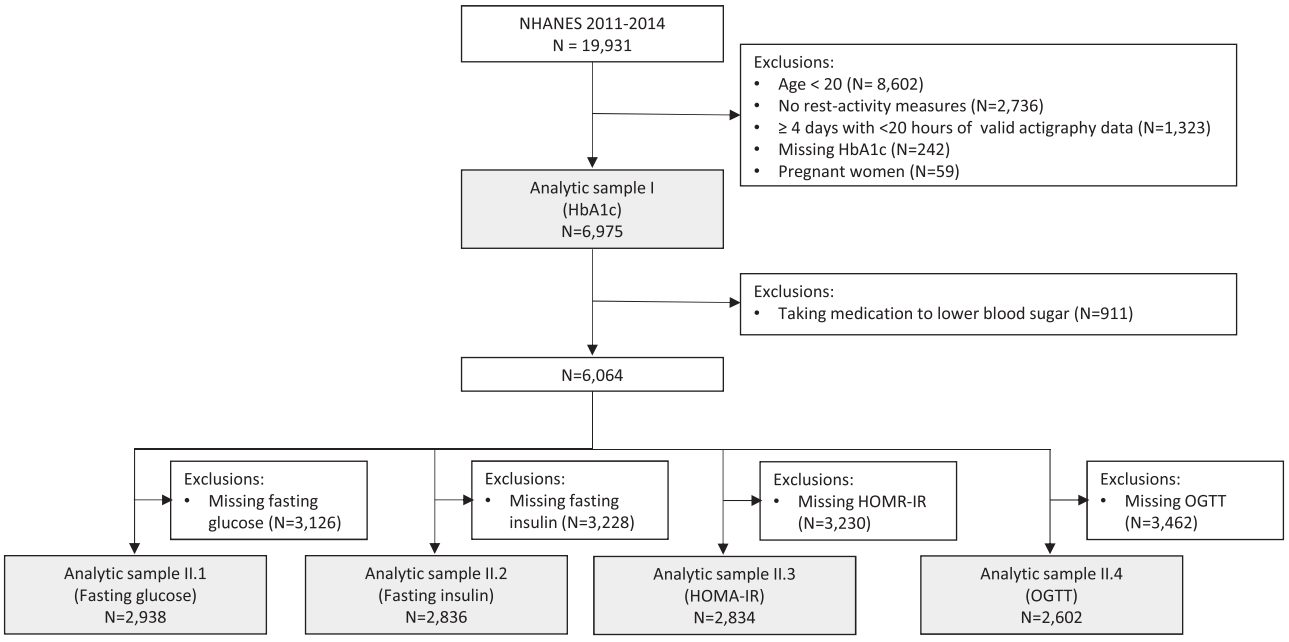

Figure 1. Flow chart showing the progression of participants to derive analytic samples for HbA1c (Analytic sample I), and fasting glucose, fasting insulin, HOMA-IR and OGTT (Analytic sample II.1-II.4). Abbreviations: HOMA-IR, homeostatic model assessment for insulin resistance; OGTT, oral glucose tolerance test.

category served as the reference, and presented odds ratios (OR) and 95% confidence intervals (CI). To examine the association with other glycemic markers, we used multiple linear regression and presented back-transformed geometric means and 95% CI. In a minimal model, we adjusted for age (continuous) and gender (men, women). In the full model, we additionally adjusted for race/ethnicity (non-Hispanic white, non-Hispanic black, Hispanic, others), education (less than high school, high school graduate, some college, college graduate or above), household income (<$20 k, $20 k–44.9 k, $45 k–74.9 k, $75 k+), marital status (married, not married), smoking (current smoker, former smoker, never smoker, or less than 100 cigarettes in life), alcohol consumption (<1 drink/week, 1 drink/week-<1 drink/day, 1+ drink/day), BMI (<18.5, 18.5–<25, 25–<30, 30+) and total energy intake (continuous). Given that sleep duration and physical inactivity are behavioral risk factors associated with diabetes, and both factors are integrated components of the rest-activity rhythm, we examined to what degree the results were explained by sleep and physical activity behaviors in sensitivity analysis. To do so, we examined the association between rest-activity rhythm parameters and HbA1c categories with and without adjustment for sleep duration (<7, 7–9, >9 hours) and total physical activity (continuous). To test for trend, we modeled categorical variables as continuous and evaluated this coefficient using the Wald test. We also performed subgroup analyses stratified by age, gender, race/ethnicity, and BMI, and calculated *p-interaction* between any two factors using the likelihood ratio test comparing a model with the cross-product term to one without. Because we noted that the distribution of study characteristics differed between those who were included in the analytic sample and those who were excluded because they had missing or invalid rest-activity and HbA1c data (Supplementary Table 1), we performed sensitivity analysis to evaluate whether the exclusion had an impact on the results. Specifically, we calculated a propensity score to indicate the likelihood of being excluded from the analytic sample for each participant who was aged 20 years or older and not pregnant, using multiple logistic regression including study characteristics listed in Supplementary Table 1. We then additionally adjusted for the propensity score in the full model to examine the association between rest-activity characteristics and HbA1c status. Analyses were carried out using SAS 9.4 (Cary, NC).

Results

We presented study characteristics by quintiles of F statistic in Table 1. When compared to those in the highest quintile reflecting the more robust overall rhythmicity, those in lower quintiles were more likely to be non-Hispanic black, have a

Table 1. Selected study characteristics [a] by quintiles of F statistic [b] in adults in NHANES 2011–2014.

	F Statistic					
	Q1	Q2	Q3	Q4	Q5	p-value
Age, %						.01
20–39	30.9	29.8	32.5	30.3	27.3	
40–59	35.4	36.0	39.5	39.1	43.1	
60+	33.7	34.2	28.0	30.5	29.6	
Women, %	46.0	51.9	50.4	55.1	57.2	<.0001
Race/ethnicity, %						<.0001
Non-Hispanic white	61.6	64.4	66.7	70.6	74.7	
Non-Hispanic black	17.6	13.8	10.9	9.0	4.3	
Hispanic	13.1	12.8	14.2	14.4	15.5	
Other	7.7	9.0	8.1	5.9	5.5	
Less than high school, %	16.9	16.2	14.8	15.2	16.6	<.0001
Household income<$20k, %	21.3	19.6	13.3	11.7	10.5	<.0001
Married, %	41.8	50.2	57.7	60.2	67.7	<.0001
Current smoker, %	29.8	21.5	18.9	13.1	13.6	<.0001
Alcohol, 1+ drink/day, %	13.4	13.6	15.2	16.2	14.9	0.01
Sleep duration, %						<.0001
<7 hours	45.0	42.9	46.2	45.9	45.5	
7–9 hours	23.1	30.4	33.6	36.5	41.4	
>9 hours	31.9	26.7	20.1	17.6	13.1	
Total activity count, [d]median (IQR)	8801 (6833, 11350)	9956 (8198, 11833)	10922 (9346, 12583)	11348 (9805, 13271)	12918 (11074, 14625)	<.0001
Obese, [e] %	45.6	44.1	40.3	35.6	29.4	<.0001
Total energy intake, kcal, median (IQR)						
Men	2246 (1737, 2868)	2224 (1693, 2684)	2517 (1977, 3131)	2220 (1738, 2731)	2454 (1958, 2968)	.01
Women	1716 (1321, 2157)	1686 (1341, 2094)	1709 (1411, 2128)	1783 (1424, 2203)	1759 (1448, 2121)	.69

[a]All percentages, median and IQR are weighted using sample weights.
[b]F statistic is a model fitness measure and higher values indicate stronger overall rhythmicity.
[c]*p*-values were derived from Chi-square test for categorical variables, analysis of variance for total energy intake, and Kruskal-Wallis test for total activity count.
[d]measured as the total daily sum of the Monitor-Independent Movement Summary triaxial value.
[e]Defined as body mass index ≥30.
Abbreviations: NHANES, National Health and Nutrition Examination Survey; IQR, interquartile range.

household income less than $20 k, report current smoking, long sleep duration (>9 hours), were less physically active, and were less likely to be women or married. The lower quintiles also had a higher prevalence of overweight and obesity.

In the main analytic sample, 3,448 (56.5%, weighted) had normal HbA1c, while 514 (8.3%), 1,749 (21.6%) and 1,264 (13.6%) were categorized as low HbA1c, prediabetic, and diabetic, respectively. Average rest-activity patterns according to different levels of HbA1c are presented in Supplementary Figure 1. In general, the average day-time activity level appeared lower for those with diabetes. We found that a weaker overall rhythmicity as indicated by a lower F statistic was associated with higher odds of being diabetic (Table 2) and the results remained after adjusting for sociodemographic and lifestyle factors and BMI (Model 2). Specifically, when compared to those in the highest quintile of F statistic, participants in the lowest quintile were 2.37 times more likely to be diabetic (OR $_{Q5\ vs.\ Q1}$ (95% CI), 2.37 (1.72, 3.26), *p-trend*, <.0001). In addition, other rest-activity profiles characteristic of weakened and/or disrupted rhythmicity (i.e., lower amplitude, mesor, and amplitude:mesor ratio, and later acrophase) were also positively associated with being diabetic (OR $_{Q5\ vs.\ Q1}$ (95% CI), *p-trend*: 2.44 (1.60, 3.72), < .0001; 1.39 (1.01, 1.91), .02; 2.09 (1.46, 2.99), .0001 for amplitude, mesor, and amplitude:mesor ratio, respectively). Moreover, when compared to those in the earliest quintile of acrophase, participants in the latest quintile had a 46% increase in the odds of being diabetic (OR $_{Q5\ vs.\ Q1}$ (95% CI), 1.46 (1.07, 2.00), *p-trend, 0.01*). We also found an association between higher odds of being prediabetic and lower F statistic (OR $_{Q5\ vs.\ Q1}$ (95% CI), 1.30 (1.03, 1.64), *p-trend, .003*), but no association with other rest-activity parameters. Finally, there was no association between rest-activity rhythms and low HbA1c status. The results were attenuated after adjusting for individual behavioral components of the rest-activity rhythm (sleep duration and total physical

Table 2. Associations between rest-activity rhythm characteristics and glycated hemoglobin (HbA1c) levels [a] in adults in NHANES 2011–2014.

	Glycated hemoglobin (HbA1c) levels, OR (95% CI)					
	Low vs. Normal		Prediabetic vs. Normal		Diabetic vs. Normal	
	Model 1	Model 2	Model 1	Model 2	Model 1	Model 2
F statistic						
Q1	1.39 (0.87, 2.23)	1.45 (0.92, 2.28)	1.76 (1.37, 2.25)	1.30 (1.03, 1.64)	3.85 (2.82, 5.26)	2.37 (1.72, 3.26)
Q2	1.31 (0.86, 2.01)	1.37 (0.87, 2.14)	1.72 (1.27, 2.34)	1.39 (1.03, 1.87)	3.38 (2.44, 4.69)	2.33 (1.68, 3.23)
Q3	0.99 (0.68, 1.42)	1.01 (0.71, 1.45)	1.22 (0.95, 1.56)	1.03 (0.80, 1.34)	2.12 (1.48, 3.04)	1.67 (1.16, 2.40)
Q4	1.54 (1.13, 2.11)	1.53 (1.11, 2.11)	1.48 (1.15, 1.90)	1.41 (1.10, 1.82)	1.68 (1.12, 2.52)	1.50 (0.97, 2.32)
Q5 (ref)	ref	ref	ref	ref	ref	ref
p-trend	*.36*	*.36*	*<.0001*	*.003*	*<.0001*	*<.0001*
Amplitude						
Q1	1.07 (0.69, 1.66)	1.05 (0.67, 1.64)	1.26 (0.85, 1.87)	1.10 (0.76, 1.59)	3.24 (2.19, 4.79)	2.44 (1.60, 3.72)
Q2	1.05 (0.71, 1.53)	0.96 (0.66, 1.40)	0.96 (0.76, 1.21)	0.94 (0.74, 1.19)	2.02 (1.24, 3.31)	1.89 (1.16, 3.08)
Q3	1.13 (0.81, 1.59)	1.04 (0.74, 1.46)	1.01 (0.73, 1.38)	1.08 (0.79, 1.49)	1.57 (1.09, 2.25)	1.77 (1.23, 2.56)
Q4	0.97 (0.70, 1.36)	0.89 (0.65, 1.23)	0.93 (0.68, 1.27)	1.00 (0.75, 1.33)	1.27 (0.84, 1.92)	1.41 (0.94, 2.11)
Q5 (ref)	ref	ref	ref	ref	ref	ref
p-trend	*.54*	*.75*	*.24*	*.73*	*<.0001*	*<.0001*
Mesor						
Q1	1.29 (0.85, 1.97)	1.24 (0.83, 1.87)	0.86 (0.65, 1.16)	0.88 (0.64, 1.21)	1.54 (1.16, 2.05)	1.39 (1.01, 1.91)
Q2	1.26 (0.87, 1.83)	1.25 (0.85, 1.85)	0.81 (0.61, 1.06)	0.89 (0.67, 1.18)	1.14 (0.86, 1.49)	1.26 (0.97, 1.64)
Q3	1.25 (0.91, 1.73)	1.24 (0.90, 1.71)	0.82 (0.63, 1.07)	0.90 (0.68, 1.18)	0.89 (0.60, 1.32)	1.00 (0.68, 1.46)
Q4	0.94 (0.67, 1.32)	0.91 (0.66, 1.25)	0.69 (0.53, 0.91)	0.77 (0.59, 1.01)	0.87 (0.61, 1.26)	1.02 (0.71, 1.45)
Q5 (ref)	ref	ref	ref	ref	ref	ref
p-trend	*.07*	*.09*	*.69*	*.76*	*<.0001*	*.02*
Amplitude:Mesor						
Q1	0.98 (0.69, 1.39)	0.97 (0.69, 1.36)	1.28 (0.92, 1.77)	1.13 (0.82, 1.56)	2.63 (1.89, 3.66)	2.09 (1.46, 2.99)
Q2	0.75 (0.55, 1.00)	0.68 (0.52, 0.90)	0.93 (0.69, 1.26)	0.98 (0.72, 1.33)	1.35 (0.87, 2.09)	1.44 (0.93, 2.23)
Q3	1.14 (0.82, 1.59)	1.06 (0.76, 1.48)	0.89 (0.61, 1.28)	0.99 (0.69, 1.42)	1.13 (0.79, 1.61)	1.29 (0.92, 1.81)
Q4	0.83 (0.54, 1.26)	0.75 (0.50, 1.13)	0.86 (0.64, 1.15)	0.97 (0.71, 1.32)	1.10 (0.77, 1.57)	1.30 (0.90, 1.89)
Q5 (ref)	ref	ref	ref	ref	ref	ref
p-trend	*.66*	*.50*	*.20*	*.57*	*<.0001*	*.0001*
Acrophase						
Q1 (ref)	ref	ref	ref	ref	ref	ref
Q2	0.95 (0.61, 1.48)	0.93 (0.60, 1.42)	0.84 (0.66, 1.07)	0.90 (0.70, 1.14)	1.08 (0.69, 1.69)	1.22 (0.82, 1.83)
Q3	0.98 (0.66, 1.46)	0.96 (0.66, 1.41)	0.96 (0.80, 1.17)	0.98 (0.79, 1.20)	1.06 (0.79, 1.41)	1.16 (0.85, 1.58)
Q4	0.76 (0.54, 1.06)	0.74 (0.53, 1.04)	1.05 (0.85, 1.30)	1.03 (0.84, 1.27)	1.14 (0.82, 1.59)	1.18 (0.87, 1.60)
Q5	0.86 (0.56, 1.32)	0.83 (0.55, 1.25)	1.00 (0.81, 1.22)	0.84 (0.66, 1.07)	1.72 (1.25, 2.38)	1.46 (1.07, 2.00)
p-trend	*.26*	*.20*	*.32*	*.55*	*.001*	*.01*

[a] HbA1c level groups are defined as: low (*N* = 514), <5%; normal (*N* = 3448), 5–5.6%; prediabetic (*N* = 1749), 5.7–6.4%; diabetic (*N* = 1264), ≥6.5% or self-reported diagnosis of diabetes or use of diabetes medication.

Model 1: adjusted for age and gender.

Model 2: adjusted for variables in Model 1 and race/ethnicity, education, household income, marital status, smoking, alcohol consumption, BMI, and total energy intake.

Abbreviations: BMI, body mass index; CI, confidence interval; NHANES, National Health and Nutrition Examination Survey; OR, odds ratio.

activity), but the association between the F statistic and diabetes remained statistically significant (OR $_{Q5\ vs.\ Q1}$ (95% CI), 1.69 (1.15, 2.49), *p-trend*, .001). Most of the other associations also remained qualitatively similar (Supplementary Table 2). The results were also robust to the adjustment of propensity score for exclusion due to missing or invalid rest-activity and HbA1c data (Supplementary Table 3).

We performed subgroup analysis for the association between rest-activity rhythms and the odds of being diabetic. The association between a lower overall rhythmicity (F statistic) and higher odds for diabetes was observed across all age, gender, race/ethnicity, and BMI groups (Figure 2 and Table 3). Moreover, the association appeared to be larger for the younger age group and people with BMI<25 compared with other groups, although the *p*-value for interaction was only of borderline statistical significance. Additional subgroup results for amplitude, mesor, amplitude:mesor ratio, and acrophase are presented in Supplementary Tables 4–7. Overall, the results were mostly similar across subgroups, suggesting a relationship between weakened rhythmicity and higher odds of diabetes. On the other hand, we also observed that the results for amplitude and amplitude:mesor ratio appeared stronger among non-Hispanic white and Hispanic participants, but weaker among blacks and Asians, while the association between a later acrophase and diabetes seemed to be more pronounced and had larger effect sizes among Asians. However, due to the large number of tests, these subgroup differences could be due to chance alone.

We presented the associations between rest-activity parameters and fasting glucose, fasting insulin, HOMA-IR, and OGTT results in Table 4. The overall patterns of the results were consistent with that for HbA1c. When compared to the highest quintile, the lower quintiles of F statistic were associated with impaired glycemic control, as evidenced by higher fasting glucose (*p-trend, .03*), fasting insulin (*p-trend, .002*), HOMA-IR (*p-trend, .0003*), and OGTT results (*p-trend, < .0001*). The results for amplitude, mesor, and amplitude:mesor ratio consistently showed that lower values of these rest-activity rhythm characteristics were associated with impaired glycemic control. In addition, later acrophase was associated with fasting insulin and HOMA-IR, but not fasting glucose or OGGT results.

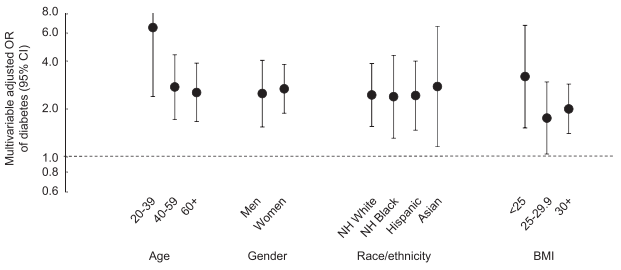

Figure 2. Associations between F statistic and diabetes [a] in adults in NHANES 2011–2014, according to age, gender, race/ethnicity and BMI. Models were adjusted for age, gender and race/ethnicity, education, household income, marital status, smoking, alcohol consumption, BMI, and total energy intake. All models were adjusted for sample weights. [a] Diabetes was defined as ≥6.5% or self-reported diagnosis of diabetes or use of diabetes medication. Abbreviations: BMI, body mass index; CI, confidence interval; NHANES, National Health and Nutrition Examination Survey; OR, odds ratio.

Discussion

In a nationally representative sample of noninstitutionalized US adults, we found that actigraphy-measured rest-activity parameters were associated with markers of glycemic control. The overall results suggested that diabetes and impaired glycemic control were more prevalent among participants with weaker rest-activity rhythms. We found these associations to be robust across populations with different sociodemographic characteristics and BMI status. Notably, weaker rest-activity rhythm was associated with diabetes across all racial/ethnic groups.

Our study findings contribute to and expand the current literature by linking weakened rest-activity rhythms to diabetes in a sociodemographically diverse sample of US adults. Earlier evidence on disrupted rest-activity rhythms and diabetes in human populations came from studies focusing on night shift workers, a population that often experience severe circadian misalignment and disruptions in rest-activity due to shift work: A meta-analysis estimated that shift work was associated with a modest increase (OR (95% CI), 1.09 (1.05, 1.12)) in diabetes risk [19]. More recently, the ubiquitous use of around-the-clock activity tracking, usually with wrist actigraphy, has provided an opportunity to characterize more subtle variations in rest-activity rhythms in the general population. A limited but growing number of studies have used actigraphy data to investigate characteristics of rest-activity rhythms in relation to metabolic health outcomes, including diabetes. For example, in a recent analysis in the Osteoporotic Fractures in Men (MrOS) study, we found that overall rhythmicity as measured by F statistic, as well as amplitude and mesor were all inversely associated with fasting insulin and HOMA-IR. Moreover, a lower amplitude and later acrophase were associated with higher odds of diabetes in older men in the MrOS study [10]. Among older men and women in the Rush Memory and Aging Project, Sohail et al. reported that reduced regularity of rest-activity rhythms was associated with higher odds of having metabolic syndrome and diabetes [8]. In addition, in multiple studies, weakened rhythmicity parameters derived from actigraphy data associated with higher BMI [9, 20, 21]. Our findings in the NHANES sample, which showed a relationship between rest-activity rhythm characteristics and multiple glycemic markers, are largely consistent with earlier analyses using convenience study samples. This suggests that rest-activity rhythm characteristics measured by actigraphy may be a robust behavioral marker for metabolic outcomes such as diabetes.

A unique strength of our study lies in its diverse and nationally representative study sample. Homogenous study samples are a major limitation of many earlier studies. Most of the aforementioned studies included older adults who were predominantly white and of higher-than-average socioeconomic positions, and therefore the findings may not be applicable to populations with different sociodemographic characteristics. Moreover, to the best of our knowledge, no previous study has directly compared the relationships between rest-activity parameters and metabolic outcomes across different age, gender, racial/ethnic groups in a representative sample of US adults. Our study addresses this gap by using recently released NHANES data, which enabled us to conduct subgroup analysis according to multiple individual characteristics. On one hand, the relationship between weaker rest-activity rhythms and diabetes appeared to be fairly robust across different subgroups. This suggests that actigraphy-derived parameters like the F statistic

Table 3. Associations (adjusted OR (95% CI)) between F statistic and diabetes [a] in adults in NHANES 2011–2014, stratified by age, gender, race/ethnicity and BMI.

	F Statistic						
	Q1	Q2	Q3	Q4	Q5	p-trend	p-interaction
Age, years							.08
20–39	6.51 (2.40, 17.69)	4.47 (1.38, 14.53)	2.58 (0.79, 8.49)	2.87 (1.07, 7.65)	ref	<.0001	
40–59	2.71 (1.69, 4.35)	3.12 (2.08, 4.69)	2.50 (1.46, 4.26)	1.55 (0.86, 2.82)	ref	<.0001	
60+	2.51 (1.65, 3.81)	2.02 (1.35, 3.04)	1.52 (0.95, 2.45)	1.28 (0.82, 2.00)	ref	<.0001	
Gender							.54
Men	2.46 (1.52, 3.97)	1.99 (1.27, 3.12)	1.51 (0.92, 2.48)	1.15 (0.61, 2.16)	ref	<.0001	
Women	2.63 (1.83, 3.76)	2.56 (1.68, 3.91)	2.14 (1.44, 3.19)	1.62 (0.97, 2.71)	ref	<.0001	
Race/ethnicity							.50
NH White	2.39 (1.49, 3.83)	2.45 (1.63, 3.69)	1.90 (1.23, 2.93)	1.49 (0.85, 2.62)	ref	<.0001	
NH Black	2.40 (1.32, 4.36)	1.89 (1.14, 3.12)	1.59 (0.91, 2.78)	1.18 (0.56, 2.48)	ref	<.0001	
Hispanic	2.34 (1.40, 3.92)	1.68 (0.97, 2.90)	1.39 (0.73, 2.65)	1.12 (0.63, 2.02)	ref	<.0001	
Asian	2.84 (1.20, 6.73)	2.82 (1.28, 6.25)	2.32 (1.04, 5.19)	1.36 (0.59, 3.10)	ref	.002	
BMI, kg/m^2							.05
<25	3.20 (1.52, 6.73)	2.78 (1.60, 4.83)	3.67 (1.83, 7.36)	1.82 (0.93, 3.56)	ref	.0002	
25–29.9	1.75 (1.04, 2.96)	1.89 (1.20, 2.99)	1.81 (1.10, 2.97)	1.58 (0.90, 2.76)	ref	.02	
30+	2.00 (1.40, 2.87)	1.79 (1.23, 2.61)	1.25 (0.74, 2.09)	1.00 (0.57, 1.75)	ref	<.0001	

[a] Diabetes was defined as ≥6.5% or self-reported diagnosis of diabetes or use of diabetes medication.
Models are adjusted for age, gender, race/ethnicity, education, household income, marital status, smoking, alcohol consumption, BMI, and total energy intake. Stratification variables were not included in their respective subgroup analyses. All models are adjusted for sample weights.
Abbreviations: BMI, body mass index; CI, confidence interval; NH, non-Hispanic; NHANES, National Health and Nutrition Examination Survey; OR, odds ratio.

for the overall rhythmicity may serve as useful behavioral markers in a wide range of populations. On the other hand, we also noted group difference in the association between certain rest-activity parameters and metabolic health. Rest-activity rhythm is partially governed by the internal circadian rhythm and it has been well established that circadian rhythms change over age and differ between men and women [22]. Differences in internal circadian rhythm properties, including phase and period, have also been reported between Americans of African and European descent [23]. Moreover, rest-activity rhythms are also shaped by numerous environmental and individual factors such as work schedules, living conditions, social interactions, and personal beliefs and choices, all of which may differ across sociodemographic groups. Indeed, a recent study reported considerable differences in rest-activity rhythm patterns across different sociodemographic groups [24]. It is important to examine how potential differences in rest-activity rhythms in different populations may have contributed to health disparities, an area that remains largely understudied. Moreover, studies focusing on evaluating the strength of the association of rest-activity parameters with health outcomes in specific populations will also provide valuable information for developing tailored algorithms for health monitoring and risk prediction based on actigraphy-based activity measures.

A relationship between weakened and/or disrupted rest-activity rhythms and diabetes is supported by mechanistic studies showing a strong link between circadian rhythms and glycemic control. Earlier studies using lab protocols to separate the influence of internal circadian rhythms from that of environmental cues demonstrated a robust circadian pattern in glucose level and tolerance [25, 26]. Moreover, human subjects who experienced lab-induced circadian misalignment exhibited increases in glucose and insulin levels consistent with impaired glucose regulation and insulin sensitivity [26]. In addition, experimental studies in animals and observational studies in human populations have reported a relationship between obesity and metabolic dysfunction and exposure to light at night, a potent disruptor of circadian rhythms [27]. Finally, animal studies also showed that circadian gene mutations led to impaired beta-cell function and the development of diabetes in mice [28]. Taken together, evidence from mechanistic and epidemiological studies suggests that people with more severe circadian disruptions and weakened circadian rhythms may be more likely to have impaired glucose metabolism. We expand upon these findings with a more representative sample, and showed consistent associations between rest-activity rhythms and metabolic health across subpopulations with varied sociodemographic characteristics. However, it is noteworthy that our study did not directly measure circadian rhythms, and as discussed above, rest-activity patterns are shaped by numerous internal and external factors. To further clarify the relationship among circadian function, rest-activity behavioral patterns, and metabolic health, future studies should investigate whether interventions to improve circadian function and rest-activity rhythmicity lead to metabolic benefits in human populations, particularly among disadvantaged populations who are at elevated risks for metabolic disorders and face more challenges in establishing and maintaining a healthy profile of rest-activity rhythms.

Besides the large and diverse sample, our study has several additional strengths. We defined four outcome categories using HbA1c, including prediabetic and low HbA1c status, because previous studies showed that these conditions may also be associated with substantial increases in mortality [16, 29]. We found that the association with rest-activity rhythms was only observed for diabetes, not prediabetic or low HbA1c status. This finding suggests that the relationship between circadian disruption and metabolic dysfunction may not be linear, but become stronger with more extreme impairment in glycemic control. In addition, we included multiple glycemic markers, including fasting glucose, insulin, and HOMA-IR, as well as OGTT results. The consistency in the results suggest that the associations

Table 4. Adjusted associations [a] between rest-activity characteristics and markers of glucose metabolism and insulin resistance in adults who did not take medications to lower blood sugar in NHANES 2011–2014.

	Adjusted geometric mean (95% CI) [b]			
	Fasting glucose (mg/dL)	**Fasting insulin (uU/mL)**	**HOMA-IR**	**OGTT (mg/dL)**
N	2794	2697	2697	2602
F statistic				
Q1	100.68 (97.68, 103.76)	10.95 (9.49, 12.62)	2.71 (2.31, 3.19)	118.59 (111.13, 126.57)
Q2	101.16 (98.42, 103.98)	11.10 (9.98, 12.34)	2.77 (2.46, 3.12)	110.95 (105.03, 117.21)
Q3	100.09 (97.25, 103.01)	10.12 (9.19, 11.14)	2.50 (2.22, 2.81)	109.11 (102.98, 115.63)
Q4	99.30 (96.66, 102.00)	9.57 (8.58, 10.68)	2.35 (2.07, 2.65)	109.13 (101.95, 116.8)
Q5 (ref)	98.04 (95.77, 100.38)	8.61 (7.67, 9.66)	2.09 (1.83, 2.39)	103.49 (97.58, 109.76)
p-trend	.03	.0002	.0003	<.0001
Amplitude				
Q1	101.40 (98.59, 104.30)	11.13 (9.87, 12.68)	2.79 (2.43, 3.21)	117.92 (111.05, 123.97)
Q2	102.54 (99.55, 105.61)	11.59 (10.49, 12.94)	2.95 (2.61, 3.34)	116.75 (112.17, 122.73)
Q3	98.50 (96.17, 100.89)	9.39 (8.41, 10.49)	2.28 (2.02, 2.58)	108.85 (102.51, 116.75)
Q4	97.86 (95.59, 100.16)	9.30 (8.33, 10.49)	2.26 (2.00, 2.57)	105.64 (99.48, 111.05)
Q5 (ref)	99.30 (96.69, 101.98)	8.94 (7.92, 10.07)	2.19 (1.91, 2.50)	102.51 (96.54, 107.77)
p-trend	.002	<.0001	<.0001	<.0001
Mesor				
Q1	101.49 (98.49, 105.64)	11.52 (10.23, 12.96)	2.89 (2.52, 3.31)	117.92 (111.05, 125.21)
Q2	99.48 (97.51, 101.49)	10.61 (9.39, 11.99)	2.61 (2.28, 2.98)	108.85 (102.51, 115.58)
Q3	99.48 (96.54, 101.49)	9.69 (8.60, 10.92)	2.38 (2.08, 2.72)	106.70 (100.48, 112.17)
Q4	99.48 (96.54, 101.49)	8.90 (7.97, 9.95)	2.19 (1.92, 2.49)	109.95 (104.58, 115.58)
Q5 (ref)	98.49 (95.58, 101.49)	9.04 (7.83, 10.45)	2.21 (1.88, 2.60)	105.64 (97.51, 113.30)
p-trend	.18	<.0001	<.0001	0.003
Amplitude:mesor				
Q1	101.49 (98.49, 104.58)	10.59 (9.30, 12.06)	2.66 (2.29, 3.10)	115.32 (108.14, 122.97)
Q2	100.48 (98.49, 103.54)	10.18 (8.94, 11.47)	2.51 (2.20, 2.89)	113.22 (106.74, 120.09)
Q3	98.49 (95.58, 101.49)	10.18 (9.21, 11.36)	2.48 (2.20, 2.83)	108.40 (101.74, 115.49)
Q4	98.49 (96.54, 101.49)	9.30 (8.33, 10.38)	2.27 (1.99, 2.59)	109.46 (103.71, 115.54)
Q5 (ref)	99.48 (96.54, 102.51)	9.58 (8.50, 10.80)	2.34 (2.05, 2.66)	103.48 (97.02, 110.38)
p-trend	.04	.02	.01	<.0001
Acrophase				
Q1 (ref)	98.52 (95.78, 101.33)	9.04 (8.61, 9.49)	2.25 (1.97, 2.58)	110.12 (103.76, 116.87)
Q2	99.70 (97.30, 102.17)	9.60 (8.86, 10.41)	2.35 (2.06, 2.69)	107.25 (101.67, 113.15)
Q3	100.31 (97.46, 103.24)	10.21 (9.55, 10.93)	2.52 (2.19, 2.90)	111.87 (105.49, 118.64)
Q4	99.65 (97.41, 101.95)	10.28 (9.89, 10.69)	2.46 (2.18, 2.77)	107.57 (101.36, 114.16)
Q5	100.34 (97.40, 103.38)	10.51 (10.02, 11.04)	2.65 (2.32, 3.04)	109.77 (103.11, 116.86)
p-trend	.12	.0002	.001	.94

[a] Models are adjusted for age, gender, race/ethnicity, education, household income, marital status, smoking, alcohol consumption, BMI, and total energy intake.
[b] Raw marker levels were log-transformed and adjusted least squares means were back-transformed.
Abbreviations: BMI, body mass index; CI, confidence interval; HOMA-IR, homeostatic model assessment of insulin resistance; NHANES, National Health and Nutrition Examination Survey; OGTT, oral glucose tolerance test.

between rest-activity rhythms and glycemic function is robust to various metabolic biomarkers.

Despite the strengths, our study also has a few limitations. First, this is a cross-sectional study and therefore we are not able to establish the temporal relationship between rest-activity rhythms and diabetes. Second, although the rest-activity rhythm is closely regulated by the circadian clock, it is also influenced by other factors and only a proxy measure of the circadian rhythm. We do not have direct measures of the internal circadian clock, such as melatonin or core body temperature, and thus cannot directly assess the relationship between circadian disruption and glycemic markers. Moreover, we also did not have measures of environmental factors that can impact circadian rhythms, such as light exposure and shift work, and could not investigate the role of these factors in shaping rest-activity patterns and their associations with metabolic health. Third, glucose and insulin levels fluctuate within the 24-hour day. Although they were measured from morning fasting blood, there could still be considerable variation in the time when blood samples were collected. This would increase variation in outcome measures, which may lead to less precise effect estimates. Fourth, rest-activity parameters were derived from the extended cosine model, which assumes a cosine-like pattern for the diurnal rest-activity rhythms. This model may not yield accurate measures of rest-activity profiles among people whose activity rhythms deviate from the presumed waveform, such as shift workers or those who are severely ill. Fifth, the number of people with diabetes were small in certain subgroups, such as the 20–39 age group, which led to unstable estimates with wide confidence intervals. Finally, we observed considerable imbalance in study characteristics between those with and without valid rest-activity and HbA1c data. Although our sensitivity analysis suggested that exclusion due to missingness in key exposure and outcome variables did not have a major impact on our results, such exclusion may have affected the representativeness of our analytic sample and thus the generalizability of our results.

In summary, our results in NHANES 2011–2014 support an association between weakened rest-activity rhythms and impaired glycemic control. Moreover, our study makes a unique contribution by

showing that this association was observed widely among different age, gender, and racial/ethnic groups. These findings invite further investigation of the role of rest-activity patterns in metabolic health, particularly in populations with diverse sociodemographic characteristics, lifestyle factors, and health status. Evidence obtained from such studies may eventually help develop algorithms using behavioral patterns and biomarkers derived from wearable devices to improve risk prediction and disease management.

Supplementary material

Supplementary material is available at *SLEEP* online.

Data and Resource Availability

NHANES datasets and documents are available at https://wwwn.cdc.gov/nchs/nhanes/.

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