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# Cross-sectional and Prospective Associations of Rest-Activity Rhythms With Metabolic Markers and Type 2 Diabetes in Older Men

https://doi.org/10.2337/dc20-0557

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## OBJECTIVE

**Disruption of rest-activity rhythms is cross-sectionally associated with metabolic disorders, including type 2 diabetes, yet it remains unclear whether it predicts impaired glucose metabolism and homeostasis. The aim of this study is to examine the cross-sectional and prospective associations between rest-activity rhythm characteristics and glycemic measures in a cohort of older men.**

## RESEARCH DESIGN AND METHODS

**Baseline rest-activity rhythms were derived from actigraphy with use of extended cosine model analysis. With subjects fasting, glucose, insulin, and HOMA of insulin resistance (HOMA-IR) were measured from blood at baseline and after ~3.5 years. Type 2 diabetes was defined based on self-report, medication use, and fasting glucose.**

## RESULTS

**In the cross-sectional analysis ($n = 2,450$), lower 24-h amplitude-to-mesor ratio (i.e., mean activity-adjusted rhythm amplitude) and reduced overall rhythmicity were associated with higher fasting insulin and HOMA-IR (all $P_{trend} < 0.0001$), indicating increased insulin resistance. The odds of baseline type 2 diabetes were significantly higher among those in the lowest quartile of amplitude (Q1) (odds ratio [OR]$_{Q1 vs. Q4}$ 1.63 [95% CI 1.14, 2.30]) and late acrophase group (OR$_{late vs. normal}$ 1.46 [95% CI 1.04, 2.04]). In the prospective analysis ($n = 861$), multiple rest-activity characteristics predicted a two- to threefold increase in type 2 diabetes risk, including a lower amplitude (OR$_{Q1 vs. Q4}$ 3.81 [95% CI 1.45, 10.00]) and amplitude-to-mesor ratio (OR 2.79 [95% CI 1.10, 7.07]), reduced overall rhythmicity (OR 3.49 [95% CI 1.34, 9.10]), and a late acrophase (OR 2.44 [1.09, 5.47]).**

## CONCLUSIONS

**Rest-activity rhythm characteristics are associated with impaired glycemic metabolism and homeostasis and higher risk of incident type 2 diabetes.**

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The rest-activity cycle, which encompasses major daily activities including sleep, physical activity, and sedentary behaviors, plays an important role in metabolic health. Low levels of physical activity and prolonged sedentary behaviors are well-established risk factors for metabolic diseases (1), and sleep disturbances in the forms of short sleep, misaligned sleep timing, and irregular sleep have also been linked to metabolic dysfunction, such as obesity (2), dyslipidemia (3), metabolic syndrome (4), and type 2

diabetes (5,6). Although previous studies have demonstrated that physical activity, sedentary behaviors, and sleep play a strong role in metabolic health, most studies have focused on individual behaviors (e.g., physical activity, sedentary behaviors, and sleep) and failed to integrate different yet interrelated daily behaviors to capture the overall pattern of 24-h rest-activity rhythms and evaluate its unique effects on metabolic health. In particular, examining the strength, regularity, and timing of the rest-activity rhythms in relation to metabolic indicators may help identify novel intervention targets for the development of preventive and therapeutic strategies to specifically improve the rhythmicity of diurnal behaviors and enhance metabolic health.

The risk for impaired glucose control and type 2 diabetes increases with age. On the other hand, aging also influences many aspects of rest-activity rhythms (7). Previous research has linked advanced age with decreases in physical activity and total sleep time and efficiency; increases in sedentary behaviors, sleep latency, and fragmentation; and shifted sleep timing including early awakening (8–12). There is also evidence suggesting that age-related disturbances in rest-activity patterns, such as reduced total sleep time and efficiency and increase in sleep fragmentation, are more pronounced in men than in women (13,14). Given the high prevalence of impairment in rest-activity rhythms in the elderly, particularly in older men, it is important to examine its potential health effects in this population.

A few recent studies used 24-h actigraphy data to examine characteristics of 24-h rest-activity rhythms in relation to metabolic health in the older population. Almost all studies focused on rhythm regularity and fragmentation and found that reduced regularity and increased fragmentation, which suggest impaired rest-activity rhythms, are associated with higher BMI, metabolic syndrome, obesity, type 2 diabetes, and dyslipidemia in older men and women (15,16). Rest-activity rhythms are multidimensional, and other characteristics such as amplitude, timing, and overall shape and/or rhythmicity have been shown to be important predictors of health outcomes in the older population (17,18), but their relationships with metabolic health remain unexplored. Moreover, to the best of our knowledge, there has been no study investigating the prospective relationship between rest-activity rhythm characteristics and metabolic health in the older population. Given the temporal ambiguity of predictors and outcomes in cross-sectional studies, investigating the prospective relationship between rest-activity rhythm characteristics and metabolic health in older populations can contribute to a better understanding of causal relationships.

To address the aforementioned gaps in the literature, we studied both the cross-sectional and prospective relationships between rest-activity rhythm patterns and metabolic health outcomes in a cohort of older men. Specifically, we hypothesized that weakened rest-activity rhythms at baseline, characterized by a lower strength of rhythmicity (i.e., amplitude, amplitude-to-mesor ratio), and average level of activity (i.e., mesor), impaired overall robustness (i.e., pseudo-F statistics), and altered activity timing (i.e., acrophase), are associated with 1) poorer glycemic control (i.e., higher fasting glucose, insulin, and HOMA of insulin resistance [HOMA-IR]) and prevalent type 2 diabetes at baseline and 2) greater worsening in glycemic control and a higher risk for incident type 2 diabetes over 3.5 years of follow-up.

## RESEARCH DESIGN AND METHODS
### Study Population
The Osteoporotic Fractures in Men Study (MrOS) (https://mrosdata.sfcc-cpmc.net) is a multicenter cohort study of risk factors for osteoporosis and other aging outcomes in older men (19). Between 2000 and 2002, MrOS enrolled 5,994 community-dwelling, ambulatory men age ≥65 years from six clinical centers in the U.S. (20). The Outcomes of Sleep Disorders in Older Men Study (MrOS Sleep study) is an MrOS ancillary study that included 3,135 MrOS participants with the aim to determine the relationships of sleep and rest-activity rhythms with a broad set of health outcomes, including cardiovascular disease (CVD), cognitive decline, and falls and fractures (21). Between 2003 and 2005, the MrOS Sleep study collected objective measures of rest-activity data as well as fasting blood samples, and fasting blood samples were collected again between 2007 and 2009 during a follow-up visit for a subset of those from the baseline visit. Both the original MrOS study and ancillary studies were approved by the institutional review boards at each of the participating field sites (University of Alabama at Birmingham; University of Minnesota; Stanford University; University of California, San Diego; Oregon Health and Science University; University of Pittsburgh; and Case Western Reserve University), and written informed consent was obtained from each participant prior to enrollment.

### Assessment of Rest-Activity Rhythms
Rest-activity rhythms were recorded using the Sleep-watch-O (Ambulatory Monitoring, Inc.) actigraph. Participants were instructed to wear the device continuously on the nondominant wrist for five 24-h periods. This actigraph contains a piezoelectric linear accelerometer, which generated a voltage each time the acceleration surpassed 0.003$g$. These voltages are gathered continuously and stored in 1-min epochs. Activity data were collected using the proportional integration mode. The orientation and sensitivity of the accelerometer are optimized for highly effective sleep-wake inference from wrist activity (22,23). Rest-activity rhythm characteristics were derived by applying an extended cosine model analysis to the activity data. This method applies an antilogistic transformation to the cosine curve and fits activity data to a squared wave rather than a cosine curve (24). It has been reported that the extended cosine model is particularly useful for studying daily activity rhythms in the older population, whose activity patterns tend to deviate from a cosine shape (24). In this current analysis, we focused on five parameters: 1) amplitude measured as peak-to-nadir difference in activity of the fitted curve, an indicator of strength of rhythmicity; 2) mesor measured as minimum + 1/2 amplitude, an indicator of average activity levels; 3) amplitude-to-mesor ratio or relative amplitude, a normalized measure of rhythm strength accounting for average activity levels; 4) pseudo-F statistics, a model goodness-of-fit measure and an indicator of overall rhythmicity; and 5) acrophase measured as the time of peak activity of the fitted curve. For amplitude, mesor, amplitude-to-mesor ratio, and pseudo-F statistics, we hypothesized that a higher value will be associated with better metabolic health and categorized each variable into quartiles. For acrophase, previous studies suggested a potential U-shaped association with some health outcomes including CVD (17) and we categorized it

into three groups: early (<mean − 1 SD, before 1304 h), normal (mean ± 1 SD, between 1304 h and 1529 h), and late (>mean + 1 SD, after 1529 h). Quartiles and groups of rest-activity variables were derived using the entire sample of 3,058 men with valid rest and activity data.

## Metabolic Biomarkers and Outcomes

At both baseline and follow-up, fasting serum samples were collected in the morning, processed on the same day, and stored at −70°C. Baseline samples were collected on the same day when actigraphy recording started. Glucose was measured enzymatically with an interassay coefficient of variation of <3%, and insulin was measured by immunoenzymometric assay, with inter- and intra-assay coefficients of variation <10% (25). HOMA-IR was calculated using the algorithm of Matthews et al. (26): fasting glucose (mg/dL) × fasting insulin (μU/mL) / 405. The distributions of baseline fasting glucose, insulin, and HOMA-IR were positively skewed, and we performed log transformation to approximate a normal distribution. We also calculated the changes in fasting glucose, insulin, and HOMA-IR between baseline and follow-up among those with repeated measures of glucose and insulin, with positive values indicating an increase in marker levels and negative values indicating a decrease. The distributions of the change variables for all three metabolic markers were approximately normal, and no transformation was performed. In addition to the continuous change variable, we also derived a binary variable to examine more substantial increases in metabolic markers as the outcome. For this binary variable, we assigned a value of 1 to those in the top 25% of the change variable for each marker (based on the prospective analytic sample [details below]), and the rest were assigned 0.

At both baseline and follow-up, participants also reported history of chronic diseases including type 2 diabetes. In addition, participants were asked to bring in all prescription medications taken in the past 30 days to clinic visits for study coordinators to record information on medication use. We defined diabetes as fasting glucose ≥6.93 mmol/L, self-reported prevalent diabetes, or use of hypoglycemic medications or insulin. We further defined impaired fasting glucose as fasting glucose ≥5.50 and <6.93 mmol/L.

## Covariates

Information on sociodemographic factors (age, education, race/ethnicity, marital status) and diet was self-reported at the enrollment of the parent study MrOS. Diet was measured using the Block 98 semiquantitative food-frequency questionnaire, which has previously been validated (27). A healthy diet score was calculated using factor analysis (28). Height and weight were measured at the baseline visit of the MrOS Sleep study using standard protocols, and we calculated BMI as weight in kilograms divided by the square of height in meters (2). Lifestyle habits measured in the MrOS included smoking, alcohol use, and physical activity. Physical activity was assessed using the Physical Activity Scale for the Elderly (PASE), a brief questionnaire specifically designed to assess physical activity levels in people age ≥65 years. With PASE, we collected information on multiple occupational, household, and leisure activities and took into consideration both the frequency and duration of physical activity. A PASE composite score (range 0–400) was calculated, and higher scores indicate higher activity levels (29). A validation study showed that PASE scores correlated well with energy expenditure (30). Self-rated health and medical history of chronic diseases including cancer and CVD and depression (Geriatric Depression Scale score ≥6 [31]) were also assessed at the baseline visit of the MrOS Sleep study.

## Analytic Samples

Figure 1 presents a flowchart for deriving analytic samples for various analyses in this study. Of the 5,994 men in the original MrOS cohort, 3,135 men enrolled in the MrOS Sleep study and provided objective data on rest-activity rhythms with use of 24-h actigraphy between 2003 and 2005, which is considered the baseline for our analysis. A total of 3,058 men had actigraphy data that passed quality control measures as previously described (21). Of these, we excluded those with missing information on rest-activity rhythms (N = 9) or metabolic markers (N = 493) and/or with extreme values (within the lowest or highest 1% [N = 106]) for fasting glucose, insulin, or HOMA-IR. The ±1% cutoff points were chosen for removal of the extreme observations that could be due to measurement errors. The final analytic sample for cross-sectional analysis was 2,450 men. In sensitivity analysis, we

further removed participants who were using hypoglycemic medications or insulin at baseline (N = 190).

A second fasting blood sample was collected at a follow-up visit (2007–2009), allowing for longitudinal analysis. A total of 973 participants from the cross-sectional analysis sample had fasting glucose and insulin levels for both the baseline and the follow-up assessments. Of these, we excluded 41 men who showed extreme (within the lowest or highest 1%) changes in glucose, insulin, or HOMA-IR between baseline and follow-up, resulting in a sample of 932 men for prospective analysis for changes in metabolic markers. In the sensitivity analysis, we further removed participants using hypoglycemic medications or insulin at either baseline or follow-up (N = 110). Finally, for prospective analysis focusing on incident type 2 diabetes, we excluded those with prevalent diabetes at baseline (n = 76) from the 932 men included in the main analysis, resulting in a sample size of 861.

## Statistical Analysis

For descriptive analysis, we compared participant characteristics according to quartiles of amplitude and categories of acrophase using $\chi^2$ test (categorical variables), ANOVA (normally distributed variables), or Kruskal-Wallis test (continuous variables with nonnormal distributions). In addition to potential confounders listed below, we also compared important lifestyle and health factors, including BMI, physical activity, sleep, self-rated health, cancer, depression, and CVD.

We used multiple linear regression to estimate adjusted geometric means (log-transformed baseline markers) and β-coefficient (change in markers) with 95% CIs. We used multiple logistic regression to estimate odds ratios (ORs) for binary outcomes (diabetes vs. no diabetes, highest quartile of change vs. lower quartiles) and multinomial logistic regression to estimate relative risk ratio for categorical outcomes (diabetes, impaired fasting glucose, and no diabetes). For all regression analyses, we considered a series of models: model 1 included age as the only covariate. Model 2, which we consider our main model, included age (continuous) and other potential confounders, including study site (Birmingham, AL; Minneapolis, MN; Palo Alto, CA; Pittsburgh, PA; Portland, OR; San Diego, CA), education (less than high school, high
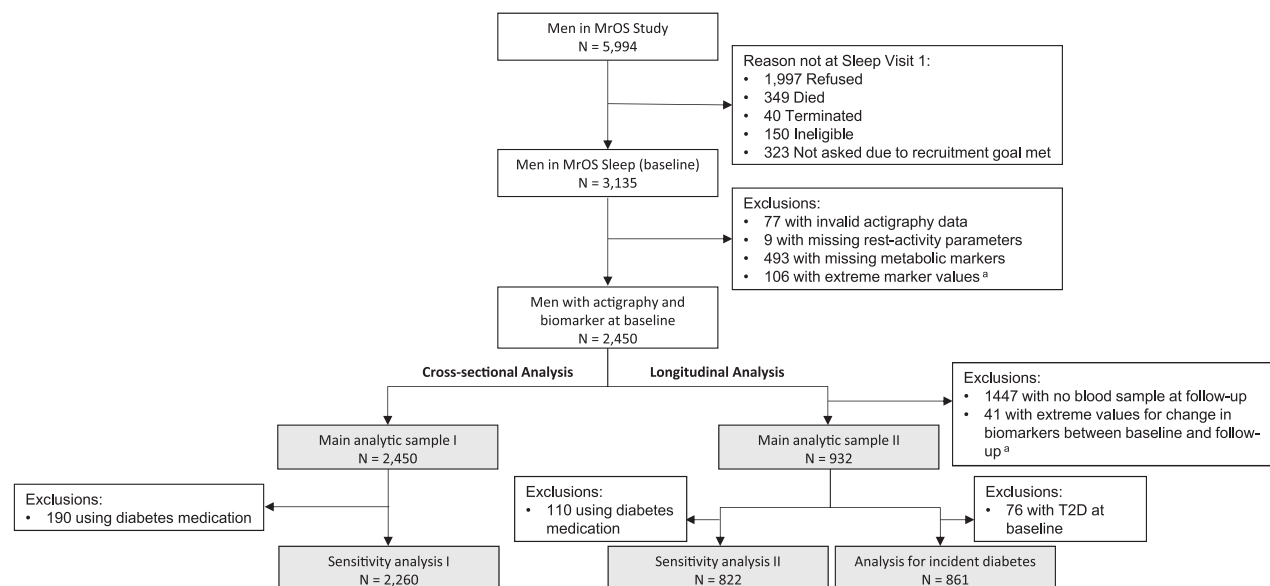
**Figure 1**—Flowchart showing the progression of participants. Gray-shaded rectangles show numbers for analytic samples for various analyses. [a]Extreme values were defined as <1% or >99% of the sample distribution. T2D, type 2 diabetes.

school, some college, college, more than college), marital status (married, not married), race (white, nonwhite), smoking status (current, past, never), alcohol consumption (<1, 1–13, ≥14 drinks/week), diet healthy index (quartiles), and season of data collection (December–February, March–May, June–August, September–November). In a separate model, we additionally included measures of individual components (physical activity score and total sleep time, sleep efficiency, and midpoint of sleep [all as continuous variables]) of the rest-activity rhythm to assess whether the associations for rest-activity rhythms are independent of measures of individual behaviors. For the analysis focusing on incident diabetes, we included baseline HOMA-IR in a separate model (model 3) to assess to what degree the results may be driven by baseline predisposition to diabetes due to insulin resistance. We also considered variables that are potential mediators (BMI) or colliders (health outcomes including history of CVD, cancer, and depression at baseline), but because adjusting for mediators and colliders is analytically problematic (32,33), we omitted these covariates in the main analysis. To test for trend, we modeled categorical variables as ordinal and evaluated this coefficient using the Wald test. Although we performed regressions for multiple exposure and outcome variables and false positives are a concern, many of our variables were highly correlated and

some of the variables were a direct function of other variables (e.g., HOMA-IR is derived from fasting glucose and insulin), and we did not control for multiple comparisons using conventional methods such as Bonferroni corrections because such methods assumes independence among tests (34). More importantly, as Greenland et al. (35) pointed out, overemphasis of measures of statistical significance such as P values can be misleading. Therefore, we avoided making judgement based on statistical significance and instead presented CIs and P values for all the associations and evaluated our results based on both effect sizes and measures of statistical significance.

## RESULTS

Study participant characteristics are presented in Table 1, according to amplitude and acrophase. We found that when compared with men in the highest quartile of amplitude, men with a lower amplitude were older, had higher BMI, and were more likely to report poorer self-rated health; lower physical activity, alcohol intake, and sleep efficiency; later sleep midpoint; and higher prevalence of CVD, depression, and cancer. When compared with normal acrophase, both early and late acrophases were associated with lower education level, nonmarried status, and less alcohol intake. Late acrophase was also associated with lower physical activity and sleep efficiency compared with normal and early acrophase groups. Finally,

there was a strong positive correlation between acrophase and midpoint of sleep.

In cross-sectional analysis, amplitude, mesor, amplitude-to-mesor ratio, and pseudo-F statistic were all inversely associated with fasting insulin and HOMA-IR ($P_{trend}$ < 0.0001 for all associations) (Table 2). Adjustment for multiple confounders had minimal impact on the findings (model 2 in Table 2). In contrast, the associations between rest-activity rhythm parameters and fasting glucose were generally weak and not statistically significant. In addition, we did not observe any association between acrophase and metabolic markers. After exclusion of participants using hypoglycemic medications or insulin, we observed little change to the results (no medication column in Table 2). These results were minimally impacted by additional adjustment for physical activity and sleep variables (Supplementary Table 1) or by exclusion of participants with chronic conditions (CVD, cancer, and depression) at baseline (data not shown).

Next, we examined rest-activity rhythms in relation to prevalent diabetes at baseline, and results are presented in Table 3. We found a trend supporting a relationship between lower quartile of amplitude and higher odds of type 2 diabetes (OR$_{Q1 \text{ vs. } Q4}$ 1.63 [95% CI 1.14, 2.30], $P_{trend}$ = 0.01). Moreover, a late acrophase was also associated with higher odds of diabetes in comparison with the normal group (OR 1.46 [95% CI 1.04, 2.04]). Analysis using the

## Table 1—Baseline (2003–2005) characteristics of older men according to quartiles of amplitude and categories of acrophase in the MrOS Sleep study

| | Amplitude | | | | | Acrophase[a] | | | |
| | Q1 | Q2 | Q3 | Q4 | P | Early | Normal | Late | P |
|---|---|---|---|---|---|---|---|---|---|
| Age, years | 78.1 (5.9) | 76.8 (5.5) | 75.8 (5.2) | 74.8 (4.9) | <0.0001[b] | 76.7 (5.3) | 76.2 (5.5) | 76.6 (5.7) | 0.28[b] |
| Education: college or higher | 53.2 | 60.1 | 56.1 | 53.0 | 0.07[c] | 45.4 | 58.2 | 54.0 | 0.0002[c] |
| Married | 79.8 | 83.6 | 86.4 | 85.4 | 0.01[c] | 82.3 | 85.3 | 77.0 | 0.0007[c] |
| White | 91.5 | 93.1 | 92.9 | 89.1 | 0.04[c] | 94.3 | 91.3 | 90.4 | 0.13[c] |
| Smoking: former or current | 61.6 | 56.8 | 59.3 | 62.3 | 0.47[c] | 63.1 | 59.4 | 59.7 | 0.07[c] |
| Alcohol: ≥1 drink/ week | 46.9 | 54.0 | 51.9 | 59.4 | <0.0001[c] | 47.7 | 55.1 | 48.1 | 0.008[c] |
| Healthy diet score | −0.06 (1.02) | 0.02 (1.05) | 0.06 (1.04) | 0.05 (0.98) | 0.10[b] | −0.01 (1.02) | 0.02 (1.02) | 0.03 (1.01) | 0.89[b] |
| BMI | 27.9 (4.0) | 27.2 (3.6) | 26.8 (3.5) | 26.7 (3.56) | <0.0001[b] | 27.6 (3.9) | 27.0 (3.6) | 27.3 (3.9) | 0.04[b] |
| Self-rated health: good/excellent | 79.6 | 86.3 | 92.0 | 90.5 | <0.0001[c] | 86.0 | 88.2 | 82.8 | 0.02[c] |
| Physical activity score | 117.9 (64.4) | 139.2 (65.0) | 157.3 (68.0) | 172.0 (72.8) | <0.0001[d] | 151.2 (73.5) | 149.6 (69.6) | 127.9 (70.4) | <0.0001[d] |
| Total sleep time, h | 6.3 (1.5) | 6.5 (1.1) | 6.5 (1.1) | 6.4 (1.1) | 0.08[d] | 6.3 (1.2) | 6.4 (1.2) | 6.3 (1.2) | 0.003[d] |
| Sleep efficiency | 0.75 (0.15) | 0.79 (0.11) | 0.80 (0.10) | 0.79 (0.11) | <0.0001[d] | 0.79 (0.12) | 0.79 (0.12) | 0.76 (0.12) | 0.005[d] |
| Sleep midpoint | 0301 h (0059 h) | 0248 h (0057 h) | 0247 h (0052 h) | 0248 h (0055 h) | <0.0001[d] | 0155 h (0059 h) | 0248 h (0040 h) | 0410 h (0042) | <0.0001[d] |
| Disease history | | | | | | | | | |
| CVD | 43.2 | 37.7 | 34.5 | 30.2 | <0.0001[c] | 36.9 | 35.3 | 41.5 | 0.10[c] |
| Depression | 10.2 | 5.8 | 4.6 | 4.8 | 0.0001[c] | 6.0 | 5.8 | 9.3 | 0.07[c] |
| Cancer | 29.3 | 30.8 | 30.2 | 22.6 | 0.004[c] | 28.6 | 28.3 | 26.8 | 0.85[c] |

Data are % or mean (SD). [a]Acrophase was categorized as early (mean − 1 SD, before 1304 h), normal (mean ± 1 SD, between 1304 h and 1529 h), and late (mean + 1 SD, after 1529 h). [b]P values were derived from ANOVA. [c]P values were derived from $\chi^2$ test. [d]P values were derived from Kruskal-Wallis test.

three-category outcome variable (diabetes, impaired fasting glucose, and normoglycemia group) showed similar findings for diabetes, but results for impaired fasting glucose were largely null (Supplementary Table 2).

In prospective analysis focusing on changes in metabolic markers as continuous outcomes, we found no association between any of the rest-activity rhythm characteristics and changes in fasting glucose, insulin, or HOMA-IR (Table 4). Exclusion of participants who reported taking hypoglycemic medications or insulin at either baseline or follow-up had little impact on the results. However, when we examined change in markers as a binary outcome to focus on more substantial increases in marker levels (an increase within the top 25%), we found evidence suggesting an association of lower amplitude and mesor with a substantial increase in HOMA-IR over follow-up ($P_{trend}$ = 0.009 for amplitude and 0.03 for mesor) (Supplementary Table 3). We also found that early acrophase was associated with 91% higher odds of a substantial increase in HOMA-IR over follow-up (OR 1.91 [95% CI 1.24, 2.95]).

Finally, we examined rest-activity rhythm characteristics and incident diabetes among men who were free of type 2 diabetes at baseline (Table 5). Despite a small number of people who developed incident diabetes (n = 48), the results seem to support a relationship between lower amplitude and a higher risk of developing diabetes. When compared with men in the highest quartile of amplitude, men in the lowest quartile were more than three times more likely to develop diabetes at follow-up (OR 3.81 [95% CI 1.45, 10.00], P = 0.001). Similar trends were also observed for amplitude-to-mesor ratio (OR 2.79 [95% CI 1.10, 7.07], P = 0.03), and pseudo-F (OR 3.49 [95% CI 1.34, 9.10], P = 0.006), indicating that this association was a reflection not just of overall activity but also of the strength of day-night rhythmicity. We also observed an association between late acrophase (compared with normal) and higher risk of incident diabetes (OR 2.44 [95% CI 1.09, 5.47]). Additional adjustment for baseline HOMA-IR (model 3 in Table 5) attenuated the results, but the trends remained similar, suggesting that the observed association could not be

fully explained by baseline differences in insulin resistance.

## CONCLUSIONS

In a cohort of older men, we found that multiple characteristics of rest-activity rhythms, particularly lower amplitude, mesor, amplitude-to-mesor ratio, and overall rhythmicity, were associated with elevated fasting insulin and higher insulin resistance at baseline. Moreover, a lower amplitude and amplitude-to-mesor ratio, reduced overall rhythmicity, and a late acrophase were also found to predict higher risk of developing type 2 diabetes over ~3.5 years follow-up. However, the relatively small number of incident diabetes cases in this population warrants confirmation in future studies.

The cross-sectional results from this study are consistent with previous investigations on rest-activity rhythms and metabolic health using 24-h actigraphy data, which also suggested that impaired rest-activity rhythms are associated with metabolic disorders. For example, in two studies of older participants, the Rush Memory and Aging Project in the U.S. and the Rotterdam Study, researchers found

**Table 2—Cross-sectional associations, geometric mean (95% CI), between rest-activity rhythm characteristics and metabolic markers**

| | Fasting glucose, mmol/L | | | Fasting insulin, pmol/L | | | HOMA-IR | | |
|---|---|---|---|---|---|---|---|---|---|
| | Model 1[a] | Model 2[b] Overall | Model 2[b] No medication[c] | Model 1[a] | Model 2[b] Overall | Model 2[b] No medication[c] | Model 1[a] | Model 2[b] Overall | Model 2[b] No medication[c] |
| **Amplitude** | | | | | | | | | |
| Q1 | 5.56 (5.47, 5.66)** | 5.55 (5.46, 5.65)** | 5.59 (5.50, 5.67) | 92.67 (88.01, 97.58)*** | 91.56 (86.98, 96.38)*** | 89.52 (84.88, 94.42)*** | 3.82 (3.61, 4.05)*** | 3.77 (3.56, 4.00)*** | 3.60 (3.39, 3.82)*** |
| Q2 | 5.44 (5.35, 5.53) | 5.44 (5.35, 5.53) | 5.5 (5.42, 5.59) | 87.35 (83.07, 91.84)*** | 87.46 (83.22, 91.91)*** | 85.88 (81.58, 90.41)*** | 3.53 (3.33, 3.73)*** | 3.54 (3.34, 3.74)*** | 3.40 (3.21, 3.60)** |
| Q3 | 5.42 (5.33, 5.51) | 5.43 (5.34, 5.52) | 5.51 (5.42, 5.59) | 81.17 (77.20, 85.34) | 80.50 (76.60, 84.59) | 79.67 (75.71, 83.84) | 3.26 (3.08, 3.46) | 3.24 (3.07, 3.43) | 3.16 (2.98, 3.34) |
| Q4 (ref) | 5.42 (5.36, 5.48) | 5.42 (5.36, 5.48) | 5.34 (5.28, 5.39) | 79.08 (76.28, 81.98) | 79.08 (76.28, 81.98) | 78.58 (75.70, 81.58) | 3.18 (3.05, 3.31) | 3.18 (3.05, 3.31) | 3.11 (2.98, 3.24) |
| $P_{\text{trend}}$ | 0.005 | 0.007 | 0.09 | <0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.0001 |
| **Mesor** | | | | | | | | | |
| Q1 | 5.50 (5.40, 5.59) | 5.52 (5.43, 5.62) | 5.39 (5.30, 5.47) | 88.83 (84.40, 93.50)*** | 88.50 (84.12, 93.12)*** | 86.61 (82.16, 91.31)** | 3.62 (3.41, 3.83)*** | 3.62 (3.42, 3.84)*** | 3.46 (3.26, 3.67)** |
| Q2 | 5.41 (5.32, 5.50) | 5.43 (5.35, 5.53) | 5.34 (5.26, 5.42) | 85.80 (81.59, 90.22)* | 86.02 (81.85, 90.39)** | 85.20 (80.95, 89.69)** | 3.44 (3.25, 3.64)* | 3.46 (3.27, 3.66)* | 3.37 (3.19, 3.57)* |
| Q3 | 5.44 (5.35, 5.54) | 5.45 (5.36, 5.54) | 5.37 (5.29, 5.45) | 82.16 (78.13, 86.40) | 81.48 (77.54, 85.63) | 80.52 (76.51, 84.75) | 3.31 (3.13, 3.51) | 3.29 (3.11, 3.48) | 3.21 (3.03, 3.40) |
| Q4 (ref) | 5.44 (5.38, 5.51) | 5.44 (5.38, 5.51) | 5.34 (5.29, 5.40) | 80.41 (77.58, 83.34) | 80.41 (77.58, 83.34) | 79.56 (76.65, 82.57) | 3.24 (3.12, 3.38) | 3.24 (3.12, 3.38) | 3.15 (3.03, 3.28) |
| $P_{\text{trend}}$ | 0.38 | 0.12 | 0.42 | <0.0001 | <0.0001 | 0.0003 | <0.0001 | <0.0001 | 0.0003 |
| **Amplitude-to-mesor ratio** | | | | | | | | | |
| Q1 | 5.54 (5.45, 5.64)* | 5.51 (5.41, 5.60) | 5.41 (5.32, 5.49) | 91.16 (86.57, 95.98)*** | 90.83 (86.30, 95.59)*** | 88.37 (83.80, 93.19)*** | 3.75 (3.54, 3.98)*** | 3.71 (3.51, 3.94)*** | 3.54 (3.34, 3.75)*** |
| Q2 | 5.45 (5.36, 5.55) | 5.45 (5.36, 5.54) | 5.36 (5.27, 5.44) | 85.48 (81.27, 89.90)* | 85.84 (81.67, 90.21)** | 84.73 (80.48, 89.21)* | 3.46 (3.27, 3.67)* | 3.47 (3.28, 3.68)* | 3.36 (3.18, 3.56)* |
| Q3 | 5.36 (5.27, 5.45) | 5.38 (5.29, 5.47) | 5.29 (5.21, 5.37) | 81.59 (77.60, 85.79) | 82.80 (78.80, 87.00) | 81.72 (77.65, 86.00) | 3.25 (3.07, 3.44) | 3.31 (3.13, 3.50) | 3.20 (3.03, 3.39) |
| Q4 (ref) | 5.44 (5.38, 5.51) | 5.44 (5.38, 5.51) | 5.35 (5.29, 5.40) | 80.18 (77.38, 83.07) | 80.18 (77.38, 83.07) | 79.47 (76.58, 82.46) | 3.24 (3.11, 3.37) | 3.24 (3.11, 3.37) | 3.15 (3.03, 3.28) |
| $P_{\text{trend}}$ | 0.009 | 0.09 | 0.11 | <0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.0001 |
| **Pseudo-F** | | | | | | | | | |
| Q1 | 5.55 (5.45, 5.64)* | 5.52 (5.43, 5.62) | 5.41 (5.32, 5.49) | 91.33 (86.75, 96.15)*** | 90.26 (85.74, 95.02)*** | 88.23 (83.64, 93.07)*** | 3.76 (3.55, 3.99)*** | 3.71 (3.50, 3.93)*** | 3.54 (3.33, 3.76)*** |
| Q2 | 5.43 (5.34, 5.52) | 5.43 (5.34, 5.52) | 5.34 (5.26, 5.43) | 86.34 (82.10, 90.81)** | 85.78 (81.59, 90.20)** | 84.36 (80.10, 88.83)* | 3.48 (3.29, 3.69)** | 3.46 (3.27, 3.66)** | 3.34 (3.16, 3.54)* |
| Q3 | 5.38 (5.29, 5.47) | 5.38 (5.29, 5.47) | 5.31 (5.23, 5.39) | 81.22 (77.26, 85.38) | 81.57 (77.63, 85.71) | 80.38 (76.37, 84.59) | 3.25 (3.07, 3.44) | 3.26 (3.08, 3.45) | 3.17 (2.99, 3.35) |
| Q4 (ref) | 5.44 (5.38, 5.51) | 5.44 (5.38, 5.51) | 5.34 (5.28, 5.40) | 79.41 (76.62, 82.30) | 79.41 (76.62, 82.30) | 79.01 (76.11, 82.01) | 3.21 (3.08, 3.34) | 3.21 (3.08, 3.34) | 3.13 (3.00, 3.26) |
| $P_{\text{trend}}$ | 0.02 | 0.05 | 0.1 | <0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.0001 |
| **Acrophase[d]** | | | | | | | | | |
| Early | 5.53 (5.43, 5.63) | 5.47 (5.37, 5.56) | 5.32 (5.24, 5.41) | 92.32 (87.66, 97.24) | 90.43 (85.87, 95.22) | 87.87 (83.31, 92.68) | 3.78 (3.57, 4.01) | 3.67 (3.46, 3.89) | 3.48 (3.28, 3.69) |
| Normal (ref) | 5.50 (5.40, 5.60) | 5.50 (5.40, 5.60) | 5.37 (5.28, 5.46) | 87.78 (83.64, 92.12) | 87.78 (83.64, 92.12) | 86.45 (82.17, 90.95) | 3.58 (3.39, 3.78) | 3.58 (3.39, 3.78) | 3.44 (3.25, 3.64) |
| Late | 5.58 (5.28, 5.91) | 5.58 (5.28, 5.91) | 5.37 (5.28, 5.46) | 94.13 (89.15, 99.39)* | 92.23 (87.36, 97.38) | 90.89 (85.85, 96.21) | 3.89 (3.65, 4.13) | 3.79 (3.57, 4.04) | 3.63 (3.41, 3.87) |
| $P_{\text{trend}}$ | 0.57 | 0.21 | 0.41 | 0.68 | 0.64 | 0.41 | 0.68 | 0.64 | 0.41 |

ref, reference. [a]Models were adjusted for age alone. [b]Models were adjusted for age, study site, education, marital status, race, smoking, alcohol, healthy diet score, and season of data collection. [c]Excluded 178 people who reported using hypoglycemic medications or insulin at baseline. [d]Acrophase was categorized as early (mean − 1 SD, before 1304 h), normal (mean ± 1 SD, between 1304 and 1529 h), and late (mean + 1 SD, after 1529 h). *P value <0.05, **P value <0.01, ***P value <0.001.

Table 3—Cross-sectional associations between rest-activity rhythm characteristics and type 2 diabetes

| | n (%) with diabetes[a] | OR (95% CI) | |
|---|---|---|---|
| | | Model 1[b] | Model 2[c] |
| **Amplitude** | | | |
| Q1 | 97 (16.5) | 1.68 (1.20, 2.36)** | 1.63 (1.14, 2.30)** |
| Q2 | 79 (12.7) | 1.21 (0.86, 1.71) | 1.23 (0.87, 1.75) |
| Q3 | 78 (12.8) | 1.20 (0.85, 1.70) | 1.21 (0.85, 1.72) |
| Q4 | 70 (11.1) | ref | Ref |
| $P_{trend}$ | | 0.004 | 0.01 |
| **Mesor** | | | |
| Q1 | 90 (15.2) | 1.33 (0.96, 1.85) | 1.41 (1.00, 1.98) |
| Q2 | 77 (12.5) | 1.04 (0.74, 1.46) | 1.10 (0.78, 1.55) |
| Q3 | 80 (13.2) | 1.10 (0.79, 1.54) | 1.11 (0.79, 1.57) |
| Q4 | 77 (12.2) | ref | Ref |
| $P_{trend}$ | | 0.13 | 0.07 |
| **Amplitude-to-mesor ratio** | | | |
| Q1 | 96 (16.4) | 1.49 (1.07, 2.07)** | 1.34 (0.96, 1.88) |
| Q2 | 81 (13.0) | 1.12 (0.89, 1.57) | 1.10 (0.78, 1.55) |
| Q3 | 72 (11.6) | 0.96 (0.68, 1.36) | 1.01 (0.71, 1.43) |
| Q4 | 75 (12.1) | ref | Ref |
| $P_{trend}$ | | 0.01 | 0.08 |
| **Pseudo-F** | | | |
| Q1 | 98 (16.7) | 1.44 (1.04, 1.99)** | 1.34 (0.96, 1.84) |
| Q2 | 78 (12.7) | 1.02 (0.73, 1.43) | 1.00 (0.71, 1.41) |
| Q3 | 69 (11.1) | 0.87 (0.61, 1.22) | 0.84 (0.59, 1.19) |
| Q4 | 79 (12.7) | ref | Ref |
| $P_{trend}$ | | 0.02 | 0.05 |
| **Acrophase[d]** | | | |
| Early | 52 (14.9) | 1.27 (0.92, 1.76) | 1.11 (0.79, 1.56) |
| Normal | 217 (12.1) | ref | ref |
| Late | 55 (17.6) | 1.55 (1.12, 2.14)* | 1.46 (1.04, 2.04)* |
| $P_{trend}$ | | 0.37 | 0.23 |

[a]Represents % of participants in the quartile or category of the rest-activity rhythm characteristic who had diabetes at baseline. [b]Models were adjusted for age alone. [c]Models were adjusted for age, study site, education, marital status, race, smoking, alcohol, healthy diet score, and season of data collection. [d]Acrophase was categorized as early (mean − 1 SD, before 1304 h), normal (mean ± 1 SD, between 1304 and 1529 h), and late (mean + 1 SD, after 1529 h). *P value <0.05, **P value <0.01.

that impaired day-to-day regularity (measured by interdaily stability) and increased fragmentation (measured by intraday variability) of rest-activity rhythms were associated with a wide range of metabolic outcomes, including obesity, metabolic syndrome, hypertension, type 2 diabetes, and dyslipidemia (15,16). In addition, a smaller study of 578 middle-aged adults (average age 52 years) found that a lower relative amplitude (the difference in activity between the highest and lowest periods divided by their sum, similar to amplitude-to-mesor ratio) was associated with higher BMI (36). In our study, we extended previous studies by reporting the associations between additional rest-activity characteristics and metabolic outcomes related to glucose control. Specifically, we found that multiple characteristics of rest-activity rhythms were associated with fasting insulin and HOMA-IR. The

associations appeared to be weaker for fasting glucose, which may be explained by β-cell compensation that leads to increased insulin secretion to keep a stable blood glucose level in the presence of insulin resistance (37). This often occurs in the early stage of impaired glucose control (i.e., in people with prediabetes). Therefore, the consistent and highly significant results for insulin and HOMA-IR suggest that disrupted rest-activity rhythms were associated with insulin resistance in older men. Despite a variety of approaches used to analyze 24-h rest-activity rhythms, from nonparametric measures such as interdaily stability and intraday variability reported previously to parametric measures in our study derived from extended cosine models, almost all of the rest-activity rhythm characteristics associated with adverse metabolic outcomes indicate weakened rhythmicity (e.g., lower interdaily

stability, higher intraday variability, lower amplitude and amplitude-to-mesor ratio, and reduced pseudo-F statistics). Taken together, findings from previous studies and this current study support our hypothesis that less robust rest-activity rhythms are associated with adverse metabolic outcomes. However, the temporal ambiguity of cross-sectional associations makes it challenging to determine whether impaired rhythmicity is a risk factor or a symptom of metabolic dysfunction.

Results from our prospective analyses are mixed. On the one hand, we found little evidence supporting an association between baseline rest-activity rhythms and prospective changes in fasting glucose, insulin, and HOMA-IR. On the other hand, we found that a lower amplitude, a lower amplitude-to-mesor ratio (relative amplitude, adjusted for mean activity), reduced overall rhythm robustness, and a later acrophase were significant predictors for the risk of developing incident type 2 diabetes over follow-up. One potential explanation for the discrepancies between the results from the two different analyses is that the relationships between rest-activity characteristics and changes in biomarker levels are not linear; instead, rest-activity characteristics may have a stronger association with more extreme changes in metabolic markers that may result in the development of diabetes. To test this hypothesis, we examined the associations between rest-activity rhythm characteristics and the likelihood of having a substantial increase (i.e., an increase in the upper 25% in our study population) in metabolic markers. Indeed, we found evidence supporting a relationship between lower amplitude and mesor and substantial increases in HOMA-IR over follow-up, which is consistent with a potential role of weakened rest-activity rhythms as a risk factor for type 2 diabetes.

We also found that an early acrophase was associated with higher odds of substantial increase in fasting glucose, insulin, and HOMA-IR. Acrophase is a measure of the timing of peak activity and is also correlated with sleep timing in our study (spearman correlation coefficient, 0.71). There is a growing literature suggesting that a later sleep timing is associated with impaired glycemic control (38,39). However, the midpoint of sleep was not significantly associated

**Table 4—Prospective associations between rest-activity rhythm characteristics and changes in metabolic markers between baseline (2003–2005) and follow-up (2007–2009)[a]**

| | Fasting glucose, mmol/L | | | Fasting Insulin, pmol/L | | | HOMA-IR | | |
| | Unadjusted mean (SD) | β (95% CI)[a] Overall | β (95% CI)[a] No medication[b] | Unadjusted mean (SD) | β (95% CI)[a] Overall | β (95% CI)[a] No medication[b] | Unadjusted mean (SD) | β (95% CI)[a] Overall | β (95% CI)[a] No medication[b] |
|---|---|---|---|---|---|---|---|---|---|
| **Amplitude** | | | | | | | | | |
| Q1 | −0.01 (0.60) | 0.03 (−0.09, 0.14) | 0.04 (−0.06, 0.15) | 4.26 (31.02) | −0.66 (−6.66, 5.34) | −0.18 (−6.42, 6.06) | 0.17 (1.50) | 0.03 (−0.25, 0.31) | 0.06 (−0.23, 0.34) |
| Q2 | 0.03 (0.58) | 0.05 (−0.06, 0.16) | 0.06 (−0.04, 0.16) | 8.04 (32.46) | 1.26 (−4.38, 6.96) | 0.72 (−5.10, 6.54) | 0.36 (1.49) | 0.12 (−0.14, 0.38) | 0.10 (−0.17, 0.36) |
| Q3 | −0.02 (0.62) | 0 (−0.11, 0.10) | 0 (−0.09, 0.10) | 5.52 (29.88) | −1.02 (−6.48, 4.44) | 0.12 (−5.52, 5.76) | 0.19 (1.36) | −0.04 (−0.29, 0.22) | 0.007 (−0.25, 0.26) |
| Q4 | −0.02 (0.56) | ref | ref | 7.32 (30.48) | ref | ref | 0.26 (1.43) | ref | ref |
| $P_{trend}$ | | 0.41 | 0.23 | | 0.94 | 0.97 | | 0.55 | 0.53 |
| **Mesor** | | | | | | | | | |
| Q1 | −0.02 (0.61) | −0.01 (−0.12, 0.11) | 0.06 (−0.05, 0.16) | 7.92 (32.22) | 2.22 (−3.66, 8.10) | 2.52 (−3.60, 8.58) | 0.32 (1.52) | 0.14 (−0.13, 0.42) | 0.20 (−0.08, 0.48) |
| Q2 | 0.02 (0.63) | 0.03 (−0.08, 0.14) | 0.06 (−0.04, 0.15) | 6.84 (32.4) | −0.48 (−6.06, 5.16) | −1.02 (−6.78, 4.80) | 0.30 (1.52) | 0.05 (−0.21, 0.31) | 0.04 (−0.23, 0.30) |
| Q3 | −0.01 (0.53) | −0.01 (−0.12, 0.10) | −0.01 (−0.11, 0.08) | 4.08 (28.5) | −2.82 (−8.34, 2.76) | −2.88 (−8.58, 2.82) | 0.14 (1.26) | −0.09 (−0.35, 0.16) | −0.11 (−0.37, 0.15) |
| Q4 | −0.02 (0.59) | ref | ref | 6.84 (30.72) | ref | ref | 0.23 (1.46) | ref | ref |
| $P_{trend}$ | | 0.89 | 0.15 | | 0.36 | 0.37 | | 0.21 | 0.10 |
| **Amplitude-to-mesor ratio** | | | | | | | | | |
| Q1 | 0 (0.61) | 0.09 (−0.03, 0.20) | 0.06 (−0.04, 0.16) | 2.82 (33.12) | −5.94 (−11.82, −0.06) | −5.28 (−11.34, 0.84) | 0.11 (1.60) | −0.18 (−0.46, 0.09) | −0.17 (−0.45, 0.11) |
| Q2 | −0.04 (0.58) | 0.02 (−0.09, 0.13) | 0.02 (−0.08, 0.12) | 3.78 (27.96) | −5.04 (−10.68, 0.60) | −5.22 (−11.04, 0.54) | 0.13 (1.28) | −0.18 (−0.44, 0.09) | −0.20 (−0.46, 0.07) |
| Q3 | 0.04 (0.58) | 0.09 (−0.01, 0.19) | 0.09 (0, 0.18) | 7.44 (31.74) | −2.34 (−7.74, 3.06) | −1.92 (−7.50, 3.60) | 0.33 (1.50) | −0.01 (−0.27, 0.24) | 0.002 (−0.25, 0.26) |
| Q4 | −0.04 (0.59) | ref | ref | 10.26 (30.48) | ref | ref | 0.38 (1.36) | ref | ref |
| $P_{trend}$ | | 0.29 | 0.48 | | 0.03 | 0.05 | | 0.10 | 0.11 |
| **Pseudo-F** | | | | | | | | | |
| Q1 | 0.05 (0.64) | 0.07 (−0.04, 0.18) | 0.07 (−0.03, 0.17) | 7.56 (34.8) | 3.36 (−2.52, 9.18) | 3.54 (−2.52, 9.60) | 0.34 (1.65) | 0.20 (−0.07, 0.47) | 0.23 (−0.04, 0.51) |
| Q2 | −0.05 (0.57) | −0.04 (−0.15, 0.07) | −0.05 (−0.15, 0.05) | 6.6 (29.58) | 1.74 (−3.90, 7.44) | 0.96 (−4.86, 6.78) | 0.25 (1.37) | 0.08 (−0.18, 0.35) | 0.04 (−0.22, 0.31) |
| Q3 | −0.04 (0.57) | −0.04 (−0.14, 0.07) | −0.03 (−0.13, 0.06) | 5.4 (31.32) | −1.32 (−6.84, 4.20) | −1.32 (−6.96, 4.38) | 0.18 (1.41) | −0.07 (−0.33, 0.19) | −0.07 (−0.33, 0.19) |
| Q4 | 0.01 (0.59) | ref | ref | 6.06 (28.32) | ref | ref | 0.23 (1.34) | ref | ref |
| $P_{trend}$ | | 0.30 | 0.26 | | 0.17 | 0.20 | | 0.10 | 0.08 |
| **Acrophase[b]** | | | | | | | | | |
| Early | 0.07 (0.63) | 0.11 (0, 0.23)* | 0.09 (−0.01, 0.20) | 8.46 (36) | 2.70 (−3.24, 8.64) | 2.82 (−3.30, 9.00) | 0.37 (1.67) | 0.17 (−0.11, 0.45) | 0.16 (−0.12, 0.44) |
| Normal | −0.03 (0.57) | ref | ref | 6.24 (30.24) | ref | ref | 0.23 (1.41) | ref | ref |
| Late | 0.02 (0.65) | 0.07 (−0.05, 0.19) | 0.09 (−0.02, 0.19) | 4.8 (28.92) | 1.26 (−4.86, 7.44) | 1.14 (−5.28, 7.62) | 0.23 (1.38) | 0.13 (−0.16, 0.41) | 0.13 (−0.17, 0.42) |
| $P_{trend}$ | | 0.52 | 0.84 | | 0.70 | 0.66 | | 0.78 | 0.81 |

ref, reference. [a]Models were adjusted for age, study site, education, marital status, race, smoking, alcohol, healthy diet score, and season of data collection. [b]Excluded 110 people who reported using hypoglycemic medications or insulin either at baseline or follow-up visit. [c]Acrophase was categorized as early (mean − 1 SD, before 1304 h), normal (mean ± 1 SD, between 1304 and 1529 h), and late (mean + 1 SD, after 1529 h).
*P value <0.05.

**Table 5—Prospective associations between rest-activity rhythm characteristics and incident type 2 diabetes among subjects without diabetes at baseline[a]**

| | n (%) with diabetes[a] | OR (95% CI) | | |
| --- | --- | --- | --- | --- |
| | | Model 1[b] | Model 2[c] | Model 3[d] |
| Amplitude | | | | |
| Q1 | 16 (8.9) | 3.58 (1.42, 9.03)* | 3.81 (1.45, 10.00)** | 2.90 (1.08, 7.78)* |
| Q2 | 16 (7.6) | 2.87 (1.15, 7.16)* | 3.33 (1.28, 8.64)* | 2.78 (1.05, 7.30)* |
| Q3 | 9 (3.8) | 1.31 (0.48, 3.59) | 1.40 (0.50, 3.93) | 1.25 (0.44, 3.57) |
| Q4 | 7 (3.0) | ref | ref | ref |
| $P_{trend}$ | | 0.001 | 0.001 | 0.01 |
| Mesor | | | | |
| Q1 | 15 (7.8) | 2.41 (0.99, 5.87) | 2.29 (0.91, 5.81) | 1.92 (0.74, 4.97) |
| Q2 | 14 (6.4) | 1.85 (0.76, 4.50) | 2.14 (0.84, 5.47) | 1.80 (0.69, 4.71) |
| Q3 | 11 (4.8) | 1.33 (0.52, 3.36) | 1.35 (0.52, 3.52) | 1.34 (0.50, 3.59) |
| Q4 | 8 (3.7) | ref | ref | ref |
| $P_{trend}$ | | 0.04 | 0.05 | 0.15 |
| Amplitude-to-mesor ratio | | | | |
| Q1 | 15 (8.3) | 2.63 (1.09, 6.39)* | 2.79 (1.10, 7.07)* | 2.33 (0.89, 6.05) |
| Q2 | 12 (5.8) | 1.80 (0.72, 4.50) | 1.83 (0.71, 4.68) | 1.98 (0.75, 5.20) |
| Q3 | 13 (5.3) | 1.57 (0.64, 2.85) | 1.62 (0.64, 4.10) | 1.55 (0.60, 4.00) |
| Q4 | 8 (3.5) | ref | ref | ref |
| $P_{trend}$ | | 0.03 | 0.03 | 0.07 |
| Pseudo-F | | | | |
| Q1 | 18 (8.9) | 3.41 (1.38, 8.43) | 3.49 (1.34, 9.10)* | 2.69 (1.01, 7.17)* |
| Q2 | 13 (6.3) | 2.25 (0.88, 5.77) | 2.29 (0.86, 6.11) | 1.98 (0.73, 5.33) |
| Q3 | 10 (4.4) | 1.48 (0.55, 3.97) | 1.53 (0.55, 4.21) | 1.30 (0.46, 3.65) |
| Q4 | 7 (3.1) | ref | ref | ref |
| $P_{trend}$ | | 0.004 | 0.006 | 0.03 |
| Acrophase[e] | | | | |
| Early | 5 (4.4) | 0.86 (0.33, 2.26) | 0.90 (0.32, 2.50) | 0.84 (0.29, 2.40) |
| Normal | 32 (5.1) | ref | ref | ref |
| Late | 11 (9.6) | 2.11 (1.02, 4.37)* | 2.44 (1.09, 5.47)* | 2.37 (1.04, 5.42) |
| $P_{trend}$ | | 0.07 | 0.06 | 0.07 |

[a]Represents % of participants in the quartile or category of the rest-activity rhythm characteristic who developed diabetes over follow-up. [b]Models were adjusted for age alone. [c]Models were adjusted for age, study site, education, marital status, race, smoking, alcohol, healthy diet score, and season of data collection. [d]Models were adjusted for variables in model 2 and baseline HOMA-IR. [e]Acrophase was categorized as early (mean − 1 SD, before 1304 h), normal (mean ± 1 SD, between 1304 and 1529 h), and late (mean + 1 SD, after 1529 h). *P value <0.05, **P value <0.01.

with metabolic markers in our study, and additionally controlling for sleep timing had little impact on the findings, suggesting that the relationships between acrophase and HOMA-IR and incident diabetes cannot be explained by the effects of sleep timing. Alternatively, timing of daytime physical activity has also been suggested to play a role in metabolic health (40), and several recent studies reported that evening exercise may be more effective in lowering glucose levels than morning exercise (41,42). However, it is worth nothing that we observed contradictory results for the association between acrophase and incident diabetes, where a later acrophase was associated with a higher risk of type 2 diabetes. Due to limited sample sizes, particularly small numbers of incident diabetes cases (only 5 and 11 participants in the early and late acrophase groups), the relationship between acrophase and metabolic health needs to be examined in future prospective studies.

The observed relationship between altered rest-activity rhythms and metabolic dysfunction may be explained by three mechanisms: First, weakened rest-activity rhythms cause metabolic dysfunction. This possibility is supported by numerous animal and human experimental studies demonstrating that disruption of circadian rhythms, a main influence on the overall pattern of 24-h rest-activity rhythms, may cause metabolic dysfunction (43). For example, disruption of the circadian clock through mutations in core circadian genes leads to impaired β-cell function and diabetes in mice (44). In human subjects, laboratory-induced circadian misalignment caused impaired glucose tolerance and reduced insulin sensitivity (45,46). However, it is worth noting that in our study, we did not have measurements of internal circadian rhythms, and it is unclear whether the observed associations reflected the adverse effects of an impaired internal circadian rhythm or were primarily driven

by altered behaviors themselves. Second, metabolic dysfunction may also impact rest-activity rhythms. For example, obesity is a well-established risk factor for sleep apnea (47), which disrupts sleep and increases sleep fragmentation and may lead to daytime sleepiness and fatigue that may also prevent individuals from engaging in exercise and other physical activities, all of which could lead to altered rest-activity patterns. In our prospective analysis focusing on incident diabetes, we observed that among men without diabetes at baseline, rest-activity rhythm characteristics predicted future development of diabetes, suggesting that impairment in rest-activity rhythms contributed to the development of metabolic dysfunction. However, it is likely that other forms of subclinical metabolic dysfunction were present at baseline, and we cannot exclude the possibility that our results were driven by the impact of metabolic dysfunction on rest-activity patterns. Finally, it is also

possible that common processes, likely associated with aging, cause both alterations in rest-activity rhythms and metabolic dysfunction. It is worth noting that the three explanations are not necessarily mutually exclusive, and future studies should focus on elucidating the multiple mechanisms that may drive the relationship between rest-activity rhythms and metabolic health. In particular, we encourage intervention studies to examine the potential benefits of strategies to enhance rest-activity rhythms, such as timed light exposure, carefully designed exercise and meal schedules, and improved sleep hygiene. Findings from such studies not only will help establish (or refute) a causal relationship between rest-activity rhythms and metabolic health but also will offer valuable evidence for clinical practice. On the other hand, our prospective results suggest that, regardless of the nature and direction of the relationship between rest-activity rhythms and metabolic health, multiple characteristics of 24-h rest-activity may serve as unique predictors of metabolic dysfunction, which should be considered by future studies that aim at developing prediction models for risks of cardiometabolic diseases.

Our study has a number of important strengths. First of all, the repeated assessments of biomarkers at both baseline and follow-up have enabled us to examine both the cross-sectional and prospective relationships between rest-activity rhythms and metabolic health. Second, we used 24-h actigraphy data to objectively measure multiple characteristics of rest-activity rhythms using an extended cosine model, an approach that is appropriate for assessing activity patterns of the older population (24). Third, we were able to assess several related yet distinct indicators of metabolic health, and our assessment of diabetes incorporated information from both self-report data and objectively measured biomarkers. Our study also has several limitations. First, the number of cases of incident diabetes was limited, probably due to a relatively short follow-up (3.5 years). Future studies with a larger sample size and longer follow-up are needed to clarify the association between rest-activity characteristics and risk of diabetes. In addition, rest-activity rhythms are shaped by both the internal circadian clock and environmental factors such as constraints on daily schedules. We did

not have measures of internal circadian rhythms, such as dim light melatonin onset, and we also did not have detailed information on participants' daily schedules or information on light exposure patterns and therefore were unable to further examine the contribution of both internal and external factors to the relationships between rest-activity rhythms and metabolic health. Finally, our group of study participants was all older men and was predominantly white, which limited the ability to generalize the findings to women, younger populations, and racial/ethnic minority groups. For example, it has been reported that men and women may have different rest-activity patterns (13,14) and different metabolic responses to circadian alterations (48); therefore, future studies are needed to examine the association of rest-activity rhythms with metabolic health in women.

In conclusion, our study found that weakened rest-activity rhythms are associated with indicators of impaired metabolic function and predict higher risk for incident diabetes. The findings, although they need to be confirmed by future prospective investigations, contribute to a growing body of literature suggesting an important role of rest-activity rhythms in metabolic health. Future studies should also focus on pinpointing the underlying mechanisms linking rest-activity rhythms with metabolic health, testing interventions targeting regulating rest-activity rhythms to improve metabolic health, and incorporating characteristics of rest-activity rhythms into algorithms to better predict metabolic disease risks.

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