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Irregular 24-hour Activity Rhythms and the Metabolic Syndrome in Older Adults

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Abstract

Circadian rhythms – near 24-hour intrinsic biological rhythms – modulate many aspects of human physiology and hence disruption of circadian rhythms may have an important impact on human health. Experimental work supports a potential link between irregular circadian rhythms and several key risk factors for cardiovascular disease including hypertension, obesity, diabetes, and dyslipidemia, collectively termed the metabolic syndrome. While several epidemiological studies have demonstrated an association between shift-work and the components of the metabolic syndrome in working-age adults, there is a relative paucity of data concerning the impact of non-occupational circadian irregularity in older women and men. To address this question, we studied 7 days of actigraphic data from 1137 older woman and men participating in the Rush Memory and Aging Project, a community-based cohort study of the chronic conditions of aging. The regularity of activity rhythms was quantified using the nonparametric interdaily stability metric, and was related to the metabolic syndrome and its components obesity, hypertension, diabetes, and dyslipidemia. More regular activity rhythms were associated with a lower odds of having the metabolic syndrome (OR=0.69, 95%CI=0.60–0.80, $p=5.8\times10^{-7}$), being obese (OR=0.73, 95%CI=0.63–0.85, $p=2.5\times10^{-5}$), diabetic (OR=0.76, 95%CI=0.65–0.90, $p=9.3\times10^{-4}$), hypertensive (OR=0.78, 95%CI=0.66–0.91, $p=2.0\times10^{-3}$), or dyslipidemic (OR=0.82, 95%CI=0.72–0.92, $p=1.2\times10^{-3}$). These associations were independent of differences in objectively measured total daily physical activity or rest, and were not accounted for by prevalent coronary artery disease, stroke, or peripheral artery disease. Moreover, more regular activity rhythms were associated with lower odds of having cardiovascular disease (OR=0.83; 95%CI=0.73–0.95, $p=5.7\times10^{-3}$), an effect that was statistically mediated by the metabolic syndrome. We conclude that irregular activity rhythms are associated with several key components of the metabolic syndrome in older community-dwelling adults, and that the metabolic syndrome statistically partially mediates the association between activity rhythms and prevalent cardiovascular disease. Although additional longitudinal and experimental studies are

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DECLARATION OF INTEREST STATEMENT

The authors report no conflicts of interest.

needed to conclusively delineate the causal relationships underlying these associations, these findings are consistent with preclinical data, and add further support for investigations of the irregularity of activity rhythms as a potential therapeutic target to decrease the burden of cardiovascular disease in older adults.

1. INTRODUCTION

Circadian rhythms – near 24-hour intrinsic biological rhythms – have a major impact on human physiology. In experimental studies, there is prominent circadian modulation of the autonomic nervous system (Scheer, Hu et al., 2010), cardiovascular physiology (Scheer, Hu et al., 2010), platelet function (Scheer, Michelson et al., 2011), endocrine function (Czeisler & Buxton, 2011), and cognition (Wyatt, Ritz-De Cecco et al., 1999) among other systems. Shift-work, a form of circadian rhythm disruption, is associated with an increased risk of accidents (Barger, Cade et al., 2005) and lost productivity (Czeisler, Moore-Ede et al., 1982). Given the circadian modulation of many aspects of human physiology, chronic circadian disruption may potentially have an important impact on human health.

Stroke, coronary artery disease, and peripheral vascular disease, collectively termed cardiovascular disease, may be among the potential consequences of circadian disruption. Experiments in model organisms and in humans suggest potential links between irregular circadian rhythms and a number of key risk factors for cardiovascular disease including hypertension, obesity, diabetes, and dyslipidemia – the “metabolic syndrome” (Buxton, Cain et al., 2012; Karatsoreos, Bhagat et al., 2011; Leproult, Holmback et al., 2014; Scheer, Hilton et al., 2009; Shi, Ansari et al., 2013; Turek, Joshu et al., 2005). Moreover, several epidemiological studies have demonstrated an association between self-reported shift-work and components of the metabolic syndrome (Barbadoro, Santarelli et al., 2013; Karlsson, Knutsson et al., 2001; Kim, Son et al., 2013; Kirsh, Cotterchio et al., 2014; Knutsson & Kempe, 2014; Lieu, Curhan et al., 2012; Monk & Buysse, 2013; Niedhammer, Lert et al., 1996; Ohira, Tanigawa et al., 2000; Ohlander, Keskin et al., 2014; Oishi, Suwazono et al., 2005; Pan, Schernhammer et al., 2011; van Amelsvoort, Schouten et al., 1999; Yamasaki, Schwartz et al., 1998).

Although adults over the age of 65 constitute the fastest growing segment of our population, community-based epidemiological studies relating circadian disruption with cardiovascular risk have focused to a large extent on working-age adults engaged in shift work. There are few data concerning the impact of non-occupational circadian irregularity on the metabolic syndrome, particularly in older adults. This is related in part to challenges in obtaining non-invasive objective measures of circadian irregularity in large numbers of ambulatory subjects in community settings. Gold standard laboratory measures of circadian rhythmicity such as rectal thermometry or serial measurements of serum markers, are invasive, perturb natural behavior, and are difficult to obtain in large numbers of individuals in an ambulatory setting. Meanwhile, self-report instruments are subjective and can be confounded by misperception and poor recall, especially in the context of cognitive impairment.

Actigraphy – the continuous measurement of rest and activity for days to weeks using a wrist-worn accelerometer – avoids many of these pitfalls. Using a modified cosinor analysis

of actigraphy data (Marler, Gehrman et al., 2006), one study reported an association between the parameters of modified cosine curves fit to actigraphic data, and incident cardiovascular disease events in older men (Paudel, Taylor et al., 2011). However, this study included only men while a majority of those over 65 are women. Moreover, the associations between circadian irregularity and the individual elements of the metabolic syndrome such as hypertension, dyslipidemia, diabetes, and obesity in older women and men remain unknown.

Using actigraphic and clinical data from 1137 older men and women participating in the Rush Memory and Aging Project, a cohort study of the chronic conditions of aging, we tested the hypothesis that greater irregularity of the 24-hour activity rhythm is associated with higher odds of having the metabolic syndrome and its components - obesity, diabetes, dyslipidemia, and hypertension – in older community-dwelling adults.

2. MATERIALS AND METHODS

2.1 Subjects

We studied participants from the Rush Memory and Aging Project – a community-based cohort study of aging with rolling admissions, which began in 1997 (Bennett, Schneider et al., 2012) and to which actigraphy was added in 2005. For these analyses, we examined data obtained at the time of the first actigraphic recording from participants who had at least one actigraphic recording with at least 7 consecutive days. A total of 1490 unique individuals participated in at least one cycle of the Rush Memory and Aging Project during or after 2005, and thus would have been eligible to undergo actigraphy. Of these, 1144 individuals agreed to undergo actigraphic recordings. After quality control (see below), 1137 individuals had at least 7 consecutive days of recording. Data from these individuals were used for these analyses.

This study was conducted in accordance with the latest version of the Declaration of Helsinki and the ethical standards of the Journal (Portaluppi, Smolensky et al., 2010) and approved by the Institutional Review Board of Rush University Medical Center. Written informed consent was obtained from all participants. All participants signed an anatomical gift act for organ donation.

2.2 Assessment of Activity Patterns

The actigraph used for this analysis was the Actical (Phillips Respironics, Bend, OR). The Actical is a wristwatch-like accelerometer that primarily measures acceleration that is parallel to the face of the device. This acceleration generates a signal that is rectified, summated across time, and recorded as an activity count for each 15-second period. Actigraphs were placed on participants' non-dominant wrist by study staff. Participants were instructed to leave the device on their wrist until staff returned to remove them after 10 days. In order to decrease participant burden, participants were not asked to keep a diary of device usage. Actigraphic records were examined visually for periods of suspected actigraph removal, and such periods were flagged. In addition to this, any period of 4 hours or greater with no movement whatsoever was also flagged as suspicious for actigraph removal. Only recordings where there were at least 7 consecutive days of recording without periods flagged

as suspicious for actigraph removal were analyzed. Where more than 7 consecutive days of recording was available, we analyzed only the first 7 days.

Interdaily stability (Sokolove & Bushell, 1978; van Someren, Hagebeuk et al., 1996; Witting, Kwa et al., 1990) is a non-parametric measure of the day-to-day stability of activity patterns. Interdaily stability provides an indication of the extent to which a periodic time series is similar in shape from cycle to cycle. Interdaily stability ranges from 0 to 1; a score of 0 indicates a complete lack of similarity from day to day, while a score of 1 indicates perfect day-to-day similarity (Figure 1). Unlike parametric approaches to assessing 24-hour rhythmicity, such as cosinor analysis (Nelson, Tong et al., 1979) or modified cosinor analysis (Marler, Gehrman et al., 2006), determination of the interdaily stability metric does not presume a particular functional form for the time series being analyzed. Moreover, it is not confounded by goodness of fit between the observed data, and the function used to parameterize it. Finally, in rodent experiments of dietary modification, reduced interdaily stability has been associated with obesity and other measures of cardiovascular risk (Bravo, Cubero et al., 2014). We calculated interdaily stability from the first 7 days each actigraphic record (containing exactly 5 weekdays and 2 weekend days) using 1-hour bins and a 24-hour period.

In addition to interdaily stability, we also calculated mean total daily activity, expressed in counts per day, mean total daily rest, expressed in hours, intradaily variability, a metric of the hour-to-hour fragmentation of the activity pattern, which ranges from 0 to 2 with higher numbers indicating greater fragmentation (Witting, Kwa et al., 1990), and kRA (Lim, Kowgier et al., 2013; Lim, Yu et al., 2011; Lim, Yu et al., 2012) a metric of sleep fragmentation, with higher numbers indicating greater fragmentation.

2.3 Assessment of the Metabolic Syndrome

Current American Heart Association guidelines (Grundy, Cleeman et al., 2005) define a person as having the metabolic syndrome if he/she has 3 or more of abdominal obesity, elevated trigylcerides, reduced high density lipoprotein, elevated blood pressure, or elevated glucose. In this study, we assessed four of these five factors as follows. Medications were determined by interview and examination of medication containers and coded by the Medi-Span system. Blood pressure was measured with mercury sphygmomanometers by trained staff. Prior to obtaining the blood pressure readings, the subjects were instructed to remain seated for five minutes. The mean of two separate seated blood pressure readings was used for the analyses. In keeping with the American Heart Association guidelines (Grundy, Cleeman et al., 2005), individuals were classified as being hypertensive if they were on anti-hypertensive medications or if they had a mean seated systolic blood pressure greater than or equal to 130 mm Hg or a mean seated diastolic blood pressure greater than or equal to 85mm Hg. High density lipoprotein and percentage of glycated hemoglobin were determined from non-fasting blood samples obtained at the time of clinical assessment. In keeping with American Heart Association guidelines (Grundy, Cleeman et al., 2005), participants were classified as having reduced dyslipidemia if their high density lipoprotein was equal to or less than 40mg/dL in men and equal to or less than 50mg/dL in women or if they were on drug treatment for dyslipidemia. In a modification of the American Heart

Association guidelines (Grundy, Cleeman et al., 2005), participants were classified as having elevated glucose if they reported a history of diabetes or if they were taking medications for elevated glucose. Fasting blood samples were not available and so fasting glucose could not be assessed. The body mass index was calculated as weight in kilograms divided by height in meters squared (kg/m^2). In keeping with World Health Organization Guidelines (WHO Expert Committee on Physical Status: the Use and Interpretation of Anthropometry., 1995), individuals with a body mass index of 30 or over were classified as obese. Fasting blood samples were not available, and so fasting triglycerides could not be assessed. In a modification of the AHA guidelines (Grundy, Cleeman et al., 2005), individuals were classified as having the metabolic syndrome if they had 3 or more of hypertension, obesity, dyslipidemia, or diabetes as defined above.

2.4 Assessment of Other Covariates

Age was calculated based on the birthdate reported at the baseline interview. Sex was determined at the baseline interview. Presence of coronary artery disease and peripheral vascular disease were determined by self-report, as was history of smoking and baseline consumption of alcohol, which was quantified in grams per week. The presence of stroke was determined by a clinician considering answers to self-report questions, an interview of the participant, and a neurological examination.

2.5 Statistical Analysis

For all analyses, interdaily stability was centered and normalized by subtracting the overall mean and dividing by the overall standard deviation. In our primary analyses, we used logistic regression models adjusted for age and sex to test for associations between the regularity of activity rhythms, quantified by the interdaily stability metric, and the presence/absence of the metabolic syndrome as defined above. We then considered an ordinal logistic regression model using the number of metabolic syndrome components (ranging from 0 to 4), as an ordinal outcome. Then, we used logistic regression models to consider each of the elements of the metabolic syndrome separately. For all these models, we first considered models that included quadratic terms for interdaily stability, and then excluded the quadratic terms in subsequent models if the p-value was not less than 0.05, which was the case for all models. Next, to exclude the possibility that any observed associations may be confounded by differences in the total daily amounts of rest and activity, we augmented these models to include terms for directly observed hours of rest per day, or total daily physical activity in counts. Fragmentation of activity and sleep may contribute to apparent decreases in regularity. To explore this, we augmented our primary models with terms to adjust for the degree of activity fragmentation, as measured by the intradaily variability metric (Witting, Kwa et al., 1990), or the degree of sleep fragmentation, as measured by the metric kRA (Lim, Yu et al., 2011). Obesity itself may plausibly mediate associations between circadian disruption and other metabolic syndrome components. To examine for this, we augmented our core models with a term for body mass index. In addition, we considered the possibility that the effect of interdaily stability on each outcome may vary as a function of BMI by considering models with a BMI × interdaily stability interaction term. Pre-existing cardiovascular disease may be associated with cardiovascular risk factors, and may also influence the activity rhythm. To explore the effect of pre-existing cardiovascular disease,

we augmented our primary models with terms to adjust for the presence/absence of stroke, coronary artery disease, and peripheral vascular disease. Dementia may be both a consequence of vascular disease and a cause of altered activity rhythms. To explore for confounding by dementia, we augmented our core models with a term for the presence/absence of dementia. Finally, we explored the effect of lifestyle factors like smoking and alcohol consumption by augmenting our core with terms for history of smoking and baseline alcohol consumption.

To ensure that any observed associations were not solely due to the cut-offs used to define hypertension, diabetes, dyslipidemia, and obesity, we then used linear regression models, adjusted for age and sex, to examine associations between the regularity of activity rhythms, quantified by the interdaily stability metric, and continuous measures of body weight, blood pressure, glycemic control, and high density lipoprotein. For these models, quadratic terms for interdaily stability were initially included, then excluded in all subsequent models if they did not have a p value less than 0.05, which was the case for all outcomes. In all participants, we tested for associations between interdaily stability and body mass index. In the subset of participants not on antihypertensive medications (n=497), we examined the relationship between interdaily stability and both systolic and diastolic blood pressure. We excluded participants taking antihypertensive medications because in individuals taking such medications, the medications are likely to have a much greater impact on blood pressure than activity rhythms, and may mask the effects of differences in activity rhythms, particularly if antihypertensives are being titrated to achieve a target blood pressure. In a similar vein, in the subset of participants not taking diabetic medications in whom measures of glycated haemoglobin were available (n=434), we examined the relationship between interdaily stability and the proportion of glycated haemoglobin. Meanwhile, in the subset of participants not taking lipid lowering medications and in whom high density lipoprotein levels were available (n=665), we examined the relationship between interdaily stability and high density lipoprotein. For all these models, we then explored the effect of potential confounders as for our logistic regression models.

Finally, we used logistic regression models adjusted for age and sex to examine the association between interdaily stability, presence of the metabolic syndrome, and prevalent cardiovascular disease. Participants were considered to have cardiovascular disease if they had at least one of stroke, coronary artery disease, or peripheral vascular disease. We first considered a logistic regression model with cardiovascular disease as the outcome and interdaily stability as the predictor, adjusted for age and sex (Model 1). Next, we considered a logistic regression model with cardiovascular disease as the outcome and presence of the metabolic syndrome as the predictor, adjusted for age and sex (Model 2). Next, we considered a model with both interdaily stability and the metabolic syndrome as predictors in the same model, adjusted for age and sex (model 3). In a scenario where the metabolic syndrome mediates the association between interdaily stability and cardiovascular disease (that is, the metabolic syndrome is in the causal pathway linking interdaily stability and cardiovascular disease), then the effect estimate for interdaily stability in Model 3 should be substantially reduced compared to Model 2 (Baron & Kenny, 1986). Finally, we considered an ordinal logistic regression model with number of cardiovascular diseases as the ordinal outcome, interdaily stability as the predictor, and adjusted for age and sex.

All statistical analyses were performed using R programming language (R Development Core Team, 2008). Visual inspection of diagnostic residual plots confirmed model assumptions.

3. RESULTS

3.1 Characteristics of the Study Participants

A total of 1137 participants were included in this study. Their clinical characteristics at the time of actigraphy are summarized in Table 1. Compared to eligible MAP cohort participants who either did not undergo actigraphy or had fewer than 7 consecutive days of actigraphy (n=353), participants who met inclusion criteria for the present study (n=1137) had a similar prevalence of the metabolic syndrome (20% vs. 20%; chi squared p=0.75), similar prevalence of hypertension (78% vs. 76%; chi squared p=0.79), similar prevalence of diabetes (15% vs. 18%; chi squared p=0.28), and similar prevalence of dyslipidemia (54% vs. 49%; chi squared p=0.64).

Interdaily stability was normally distributed and ranged from 0.10 to 0.87 with a mean (SD) of 0.55 (0.13). When only the five weekdays of each recording were considered, interdaily stability was higher with a range of 0.23 to 0.97 and a mean (SD) of 0.65 (0.13). Interdaily stability was not significantly associated with age in both bivariate (estimated effect size = 0.0006 SD change in interdaily stability per additional year of age, SE=0.0005, p=0.25) and multivariate analyses (estimated effect size = 0.006 SD change in interdaily stability per additional year of age, SE=0.004, p=0.14) adjusted for sex, prevalent vascular diseases (coronary artery disease, peripheral vascular disease, and stroke), prevalent metabolic syndrome components (hypertension, diabetes, obesity, dyslipidemia) and smoking and alcohol. Interdaily stability was not significantly associated with sex in either bivariate (estimated effect size = −0.014 SD difference in interdaily stability for male vs. female, SE=0.009, p=0.12) or multivariate analyses (estimated effect size = −0.013 SD difference in interdaily stability for male vs. female, SE=0.007, p=0.07) as above.

3.2 24-hour Regularity of Activity Rhythms and the Metabolic Syndrome

Of the 1137 participants, 232 had the metabolic syndrome. We first examined the relation of each SD higher interdaily stability with the odds of the metabolic syndrome in a logistic regression model adjusted for age and sex. We found that each SD of higher interdaily stability was associated with an odds ratio of 0.69 of having the metabolic syndrome (Table 2 Column 1 Model A). This effect was independent of variation in total daily activity, total daily rest, activity fragmentation, sleep fragmentation, or body mass index (Table 2 Colum 1 Models B–H). Moreover, it was independent of the presence/absence of pre-existing stroke, coronary artery disease, or peripheral vascular disease, suggesting that the association between interdaily stability and the metabolic syndrome was not due to effects of cardiovascular disease on interdaily stability (Table 2 Column 1 Model I). This effect was also independent of the presence/absence of dementia, history of smoking, or alcohol use (Table 2 Column 1 Model J–K). In a model including all of these covariates, the effect was essentially unchanged (Table 2 Column 1 Model L) Interestingly, in a model with a BMI × interdaily stability interaction term, the interaction term was positive and significant

(estimate=0.04, SE=0.02, p=0.02) indicating that the effect of interdaily stability on the odds of having the metabolic syndrome were greatest for those with the lowest BMI. In an ordinal regression model with number of metabolic syndrome components as the outcome, each SD of higher interdaily stability was associated with lower odds of having more metabolic syndrome components (OR=0.75 of having one additional metabolic syndrome component, 95% CI 0.68–0.84, $p=1.7\times10^{-7}$ for each 1SD of higher interdaily stability), indicating that greater interdaily stability is associated not only with a lower odds of having the metabolic syndrome, but also a lower odds of having a larger number of metabolic syndrome components.

3.3 24-hour Regularity of Activity Rhythms and Components of the Metabolic Syndrome

We then conducted a series of logistic regression models for the individual components of the metabolic syndrome, adjusted for age and sex. First, we found that each SD higher interdaily stability was associated with an odds ratio of 0.73 of being obese (Table 2 Column 2 Model A). This effect was independent of differences in total daily activity and rest, or activity or sleep fragmentation, and was not accounted for by the presence/absence of pre-existing stroke, coronary artery disease, or peripheral vascular disease, or the presence/absence of dementia, or a history of smoking and weekly alcohol consumption (Table 2 Column 2 Models B–K). Including all of these covariates in a single model did not substantially attenuate the association between interdaily stability and obesity.

Next, we found that each SD higher interdaily stability was associated with an odds ratio of 0.78 of having hypertension (Table 2 Column 3 Model A). Again, this was independent of total daily physical activity and rest, or activity or sleep fragmentation (Table 2 Column 3 Models B–G). Moreover, controlling for body mass index did not substantially change this association (Table 2 Column 3 Model H), indicating that this association was not mediated by BMI. Further, this association remained significant in models adjusted for the presence/absence of pre-existing cardiovascular diseases, dementia, or a history of smoking and weekly alcohol consumption (Table 2 Column 3 Models I–K) or in a model considering all of the above covariates together (Table 3 Column 3 Model L). There was no significant interaction between BMI and interdaily stability ($p>0.05$)

Higher interdaily stability also was associated with an odds ratio of 0.76 of having diabetes (Table 2 Column 4 Model A). Adjustment for total daily activity or total daily rest, for activity fragmentation, for body mass index, for pre-existing cardiovascular diseases, for the presence/absence of dementia, or for a history of smoking and weekly alcohol consumption did not substantially change this association (Table 2 Column 4 Models B–K). However, this association was somewhat attenuated in a model considering all these covariates together (Table 2 Column 4 Model L). There was no significant interaction between BMI and interdaily stability ($p>0.05$)

In the final set of these metabolic syndrome component analyses, higher interdaily stability was associated with an odds ratio of 0.82 of having dyslipidemia (Table 2 Column 5 Model A). Addition of terms for total daily activity and rest or for the fragmentation of activity or sleep did not change this association, suggesting that the association between interdaily stability and dyslipidemia was independent of total amounts of physical activity, total rest,

or activity or sleep fragmentation (Table 2 Column 5 Models B–G). Addition of a term for body mass index did not attenuate the significance of the association between interdaily stability and dyslipidemia (Table 2 Column 5 Model H). After addition of terms for coronary artery disease, stroke, and peripheral vascular disease, a term for the presence/absence of dementia, or for a history of smoking and weekly alcohol consumption the association between interdaily stability and dyslipidemia remained significant (Table 2 Column 5 Model I–K). It also remained significant in a model considering all these covariates together (Table 2 Column 5 Model L). There was no significant interaction between BMI and interdaily stability ($p>0.05$)

3.4 24-hour Regularity of Activity Rhythms and Continuous Measures of Metabolic Syndrome Components

Next, we used linear regression models, adjusted for age and sex, to examine associations between the regularity of activity rhythms, quantified by the interdaily stability metric, and continuous measures of body weight, blood pressure, glycemic control, and high density lipoprotein. For none of the models was a BMI × interdaily stability interaction term statistically significant.

In our study cohort, each SD higher interdaily stability was associated with almost 1 point lower BMI, an association that remained significant when adjusted for total daily rest, total daily activity, sleep or activity fragmentation, the presence/absence of coronary artery disease, stroke, or peripheral vascular disease, or the presence/absence of dementia or a history of smoking and weekly alcohol consumption (Table 3 Column 1). Moreover, in participants not taking antihypertensive mediations (n=497), each SD higher interdaily stability was associated with nearly 2 mm Hg lower systolic blood pressure, and more than 1mm Hg lower diastolic blood pressure, an effect independent of the degree of activity fragmentation. These associations were somewhat attenuated in models adjusted for total daily rest, total daily activity, sleep fragmentation, BMI, or presence/absence of coronary artery disease, stroke, or peripheral vascular disease, or the presence/absence of dementia or a history of smoking and weekly alcohol consumption (Table 3 Columns 2–3). In participants without diabetes in whom measures of glycated haemoglobin were available (n=434), interdaily stability was not associated with the proportion of glycated haemoglobin (Table 3 Column 4). In a linear model considering the subset of individuals not taking lipid lowering medications, each SD higher interdaily stability was associated with an increase in HDL of more than 3mg/dL, an association that remained significant when adjusted for total daily rest, total daily activity, activity or sleep fragmentation, body mass index, the presence/absence of coronary artery disease, stroke, or peripheral vascular disease, or the presence/absence of dementia or a history of smoking and weekly alcohol consumption (Table 3 Column 5).

3.5 24-hour Regularity of Activity Rhythms, the Metabolic Syndrome, and Prevalent Cardiovascular Disease

In the final set of analyses, we sought to determine whether the metabolic syndrome would mediate (i.e. account in part for the association between) interdaily stability and the odds of cardiovascular disease. We used standard approaches to mediation as described elsewhere

(Baron & Kenny, 1986) and in our previous work (Bennett, Schneider et al., 2005). First, we demonstrated that each SD higher interdaily stability was associated with an odds ratio of 0.83 of having cardiovascular disease. By contrast, the presence of the metabolic syndrome was associated with an odds ratio of 2.49 of having cardiovascular disease. A third model evaluated all three terms together. In this model, a reduction of the effect of interdaily stability on the odds of cardiovascular disease with the maintenance of the effect of the metabolic syndrome would be consistent with mediation. In this analysis, interdaily stability was no longer statistically significant. By contrast, the effect of the metabolic syndrome on cardiovascular disease remained significant (Table 4). Finally, in an ordinal logistic regression model, each SD greater interdaily stability was associated with an OR of 0.84 for having one additional cardiovascular disease (heart disease, stroke, or peripheral vascular disease) with a 95% confidence interval of 0.73 to 0.96 and a p-value of 9.6×10^{-3}, indicating that not only is greater interdaily stability associated with a lower odds of having any cardiovascular disease, but it is also associated with a lower odds of having a larger number of cardiovascular diseases.

4. DISCUSSION

In this study of 1137 community dwelling older adults, more regular activity rhythms, measured using a robust non-parametric analysis of 7 days of ambulatory actigraphy data, were associated with lower odds of having the metabolic syndrome or its components hypertension, diabetes, dyslipidemia, and obesity. These associations were independent of differences in total daily physical activity and rest and fragmentation of activity rhythms and sleep, and were not accounted for by pre-existing coronary artery disease, stroke, or peripheral vascular disease. Moreover, the associations with hypertension, diabetes, and dyslipidemia were not accounted for by differences in body mass index. In addition, similar associations were found between more regular activity rhythms and continuous measures of blood pressure, obesity, and dyslipidemia. Finally, more regular activity rhythms were associated with lower odds of having prevalent cardiovascular disease, an effect that was statistically mediated by the metabolic syndrome. Together, these findings are compatible with the hypothesis that irregular activity rhythms may predispose to key components of the metabolic syndrome in older community-dwelling adults, and that the metabolic syndrome may be a step in the causal chain linking irregular activitiy rhythms with cardiovascular disease. Although additional longitudinal and experimental studies are needed to conclusively delineate the causal relationships underlying these associations, these findings are consistent with preclinical data, and add further support for investigations of the irregularity of activity rhythms as a potential therapeutic target to decrease the burden of hypertension, diabetes, obesity, and dyslipidemia and hence their cardiovascular consequences in older adults.

Coronary artery disease, stroke, and peripheral vascular disease, collectively called cardiovascular disease, together constitute the leading cause of mortality and neurological disability in North America (Go, Mozaffarian et al., 2013). A substantial proportion of the risk for cardiovascular disease is accounted for by a series of well-studied vascular risk factors including hypertension, dyslipidemia, elevated plasma glucose, and obesity (National Cholesterol Education Program Expert Panel on Detection & Treatment of High Blood

Cholesterol in, 2002; Yusuf, Reddy et al., 2001), collectively termed the “metabolic syndrome” (Grundy, Cleeman et al., 2005). However, these conditions are themselves the product of a series of behavioral, genetic, and environmental risk factors - the “risk factors for the risk factors”, and addressing root causes of the metabolic syndrome is a potentially important component of any strategy to decrease the population burden of cardiovascular disease.

Our results are consistent with three scenarios. In the first, irregular activity rhythms contribute to hypertension, diabetes, dyslipidemia, and excessive weight. In the second, the metabolic syndrome itself leads to irregular activity rhythms. In the third, irregular activity rhythms and hypertension, diabetes, abnormal lipids, and excessive weight are all a manifestation of an unmeasured medical disorder (i.e. an unmeasured latent variable), but are not causally related per se. Arguing against the third scenario, our key results were essentially unchanged after adjusting for the presence/absence of existing cardiovascular diseases such as stroke, coronary artery disease, or peripheral vascular disease, or for the presence/absence of dementia. With regard to the second scenario, we are aware of no evidence that diabetes, hypertension, and dyslipidemia themselves cause irregular activity rhythms independent of end organ cardiovascular disease. In model organisms, forced weight gain can influence observed activity rhythms (Bravo, Cubero et al., 2014). However, the observed associations between interdaily stability and hypertension, diabetes, and dyslipidemia in the present study were all independent of body mass index. With regard to the first scenario, there is a wealth of experimental evidence supporting a causal link between disrupted circadian rhythms, and several key components of the metabolic syndrome, both in model organisms, and in humans (Buxton, Cain et al., 2012; Karatsoreos, Bhagat et al., 2011; Leproult, Holmback et al., 2014; Scheer, Hilton et al., 2009; Shi, Ansari et al., 2013; Turek, Joshu et al., 2005). In at least some model systems, these effects seem to be a direct effect of disruption of tissue-level molecular circadian rhythms in relevant tissues. For instance, it has been demonstrated that tissue-specific disruption of molecular circadian rhythms in the pancreatic islet cells is sufficient to lead to abnormalities of insulin secretion and glucose tolerance (Marcheva, Ramsey et al., 2010).

A small number of previous studies have examined the association between age and some metabolic syndrome components (e.g. body mass index) and the stability of activity rhythms. Associations between age and greater stability of activity rhythms have previously been reported (Luik, Zuurbier et al., 2013; Monk, Petrie et al., 1994). We found no significant association. The difference may relate in large part to the much older age of the participants in our study whose mean age was 81.6 years as compared to a mean age of 62 years in one study (Luik, Zuurbier et al., 2013), and a mean age of 29.9 in another study (Monk, Petrie et al., 1994). Concordant with our study, one previous study demonstrated an association between increased body mass index and decreased stability of activity rhythms (Luik, Zuurbier et al., 2013).

The data in this study are concordant with a wealth of experimental work in model organisms and in humans which supports a potential impact of circadian disruption on key components of the metabolic syndrome including hypertension, dyslipidemia, obesity, and diabetes (Buxton, Cain et al., 2012; Karatsoreos, Bhagat et al., 2011; Leproult, Holmback et

al., 2014; Scheer, Hilton et al., 2009; Shi, Ansari et al., 2013; Turek, Joshu et al., 2005). Moreover, they build upon an existing body of epidemiological studies showing associations between shift-work and the incidence and prevalence of these factors in working age adults (Barbadoro, Santarelli et al., 2013; Karlsson, Knutsson et al., 2001; Kim, Son et al., 2013; Kirsh, Cotterchio et al., 2014; Knutsson & Kempe, 2014; Lieu, Curhan et al., 2012; Monk & Buysse, 2013; Niedhammer, Lert et al., 1996; Ohira, Tanigawa et al., 2000; Ohlander, Keskin et al., 2014; Oishi, Suwazono et al., 2005; Pan, Schernhammer et al., 2011; van Amelsvoort, Schouten et al., 1999; Yamasaki, Schwartz et al., 1998). Our results extend these previous findings in several respects. First, they show that non-occupational circadian disruption in older individuals may have an important impact on key components of the metabolic syndrome similar to that of occupational circadian disruption in working-age shift workers. Second, whereas one study had previously reported a link between parametric cosinor-based measures of actigraphic rhythmicity and incident cardiovascular diseases in older men (Paudel, Taylor et al., 2011), whether irregularity of activity rhythms is associated with the key components of the metabolic syndrome was unknown. Our results suggest that this is in fact the case, in both older men and older women. This is important because the metabolic syndrome is associated with important morbidity in its own right independent of its impact on cardiovascular disease, and many aspects of the metabolic syndrome are targetable in their own right.

Our results do not directly address the question of potential causes for differences in the stability of activity rhythms in older adults. Important biological causes may include differential susceptibility to age-related changes in the suprachiasmatic nucleus (Swaab, Van Someren et al., 1996), retinal changes leading to differences in the ability to entrain to light (Budenz, Anderson et al., 2007; Duffy, Zeitzer et al., 2007), or even age related differences in molecular circadian rhythms (Lim, Srivastava et al., 2014). Differences in social and environmental zeitgebers may also be important, including conscious behaviours such as setting and alarm clock or choosing when to eat. Indeed, our observation that interdaily stability is greater when considering weekdays alone than when considering both weekdays and weekends highlights the effect of weekday-associated environmental/social factors in maintaining a more regular activity rhythm. It is possible that different causes of irregular activity rhythms may be differentially associated with the metabolic syndrome or its components. Further studies are needed to clarify whether this is the case.

The possibility that there may be a causal link between irregular activity rhythms and the metabolic syndrome is of particular significance in that it raises the possibility that addressing irregular activity rhythms may decrease the burden of the metabolic syndrome in older persons. There is growing evidence that simple environmental and social interventions may improve the regularity of activity rhythms (Van Someren & Riemersma-Van Der Lek, 2007) including light (Dowling, Hubbard et al., 2005; Van Someren, Kessler et al., 1997) and regularly scheduled physical activity (Atkinson, Edwards et al., 2007). Regular scheduling of other zeitgebers, such as feeding, temperature, or melatonin may also be potentially helpful (Van Someren & Riemersma-Van Der Lek, 2007).

One interesting observation is that the effects of irregular activity patterns on the odds of having the metabolic syndrome were greatest in those with the lowest BMI, as indicated by

the positive BMI × interdaily stability interaction term (and negative main effect of interdaily stability). One possible interpretation is that the lower one's BMI, the more susceptible one is to the ill effects of irregular activity rhythms and vice versa. If true, this would suggest that individuals with the lowest BMI may benefit the most from interventions to improve the regularity of activity rhythms. Additional experimental work is needed to clarify whether this is indeed the case, and what the underlying mechanisms are.

In interpreting our results, a number of methodological considerations are worth considering. First, this was a cross-sectional observational study, precluding definite determination of the causal direction of the associations between the regularity of activity rhythms and the metabolic syndrome. While these findings suggest that the metabolic syndrome may mediate an association between irregular activity rhythms and cardiovascular disease, they do not preclude alternative or more complex interactions between the regularity of activity rhythms, the metabolic syndrome, and cardiovascular disease. A second methodological consideration is that the actigraphic recordings do not allow differentiation between irregular activity rhythms due to circadian clock dysfunction and irregular activity rhythms due to external factors such as irregular social schedules or environmental exposures. A third methodological consideration is that while our definition of the metabolic syndrome was based on that in the American Heart Association Guidelines, it differed in a number of respects, including the absence of fasting triglyceride and glucose measurement, and the use of BMI rather than waist circumference to determine obesity. Finally, we had an all-volunteer with a majority of individuals of European descent, potentially limiting generalizability to other populations.

This study also has several strengths. First, the relatively large sample size (n=1137) and the inclusion of both men and women allowed for the independent contributions of age, sex, and circadian irregularity to be distinguished. Second, our large-scale use of actigraphy allowed for an objective and prolonged assessment of the temporal distribution of rest and activity, avoiding confounding by incomplete or biased recall, and capturing all forms of activity irregularity (e.g. occupational and non-occupational). Third, we directly and objectively measured both total daily activity and total daily rest, as well as activity and sleep fragmentation, allowing us to distinguish the independent contributions of physical activity, rest, activity fragmentation, sleep fragmentation, and irregularity of activity patterns. Fourth, we used a non-parametric analytical approach that quantifies rhythmicity without making assumptions about the shape of the underlying time series, and is not confounded by goodness of fit or lack thereof to a particular functional form.

These results invite further investigation of the impact of irregular daily rhythms on the elements of the metabolic syndrome and on cardiovascular risk more broadly. Examination of more direct markers of circadian rhythmicity such as clock and effector gene expression in relevant organs such as adipose tissue, muscle, liver, and pancreas may allow differentiation of true disrupted circadian rhythmicity from the masking effects of environmental or social factors, and may identify the tissues responsible for mediating the effects of circadian disruption on glucose metabolism, weight regulation, blood pressure regulation, and lipid metabolism. Meanwhile, ascertainment of additional steps in the causal pathways underlying cardiovascular disease (e.g. atherosclerosis, endothelial function) may

allow a finer delineation of the physiological links between circadian disruption, the metabolic syndrome, and cardiovascular risk. Longitudinal observational studies will illuminate the temporal sequence of circadian disruption, the metabolic syndrome, and cardiovascular diseases. Ultimately studies of interventions to improve circadian rhythmicity will most definitively shed light on the causal links between circadian disruption, the metabolic syndrome, and cardiovascular diseases.

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REFERENCES

Atkinson G, Edwards B, Reilly T, Waterhouse J. Exercise as a synchroniser of human circadian rhythms: an update and discussion of the methodological problems. European journal of applied physiology. 2007; 99:331–341. [PubMed: 17165050]

Barbadoro P, Santarelli L, Croce N, Bracci M, Vincitorio D, Prospero E, Minelli A. Rotating shift-work as an independent risk factor for overweight Italian workers: a cross-sectional study. PLoS One. 2013; 8:e63289. [PubMed: 23675472]

Barger LK, Cade BE, Ayas NT, Cronin JW, Rosner B, Speizer FE, Czeisler CA. Extended work shifts and the risk of motor vehicle crashes among interns. N Engl J Med. 2005; 352:125–134. [PubMed: 15647575]

Baron RM, Kenny DA. The moderator-mediator variable distinction in social psychological research: conceptual, strategic, and statistical considerations. J Pers Soc Psychol. 1986; 51:1173–1182. [PubMed: 3806354]

Bennett DA, Schneider JA, Buchman AS, Barnes LL, Boyle PA, Wilson RS. Overview and findings from the rush Memory and Aging Project. Curr Alzheimer Res. 2012; 9:646–663. [PubMed: 22471867]

Bennett DA, Schneider JA, Wilson RS, Bienias JL, Berry-Kravis E, Arnold SE. Amyloid mediates the association of apolipoprotein E e4 allele to cognitive function in older people. J Neurol Neurosurg Psychiatry. 2005; 76:1194–1199. [PubMed: 16107349]

Bravo R, Cubero J, Franco L, Mesa M, Galan C, Rodriguez AB, Jarne C, Barriga C. Body weight gain in rats by a high-fat diet produces chronodisruption in activity/inactivity circadian rhythm. Chronobiol Int. 2014; 31:363–370. [PubMed: 24304409]

Budenz DL, Anderson DR, Varma R, Schuman J, Cantor L, Savell J, Greenfield DS, Patella VM, Quigley HA, Tielsch J. Determinants of normal retinal nerve fiber layer thickness measured by Stratus OCT. Ophthalmology. 2007; 114:1046–1052. [PubMed: 17210181]

Buxton OM, Cain SW, O'Connor SP, Porter JH, Duffy JF, Wang W, Czeisler CA, Shea SA. Adverse metabolic consequences in humans of prolonged sleep restriction combined with circadian disruption. Science translational medicine. 2012; 4:129ra143.

Czeisler, CA.; Buxton, OM. The Human Circadian Timing System and Sleep-Wake Regulation. In: Kryger, MH.; Roth, T.; Dement, WC., editors. Principles and Practice of Sleep Medicine. St. Louis, MO: Saunders; 2011.

Czeisler CA, Moore-Ede MC, Coleman RH. Rotating shift work schedules that disrupt sleep are improved by applying circadian principles. Science. 1982; 217:460–463. [PubMed: 7089576]

Dowling GA, Hubbard EM, Mastick J, Luxenberg JS, Burr RL, Van Someren EJ. Effect of morning bright light treatment for rest-activity disruption in institutionalized patients with severe Alzheimer's disease. International psychogeriatrics / IPA. 2005; 17:221–236. [PubMed: 16050432]

Duffy JF, Zeitzer JM, Czeisler CA. Decreased sensitivity to phase-delaying effects of moderate intensity light in older subjects. Neurobiol Aging. 2007; 28:799–807. [PubMed: 16621166]

Go AS, Mozaffarian D, Roger VL, Benjamin EJ, Berry JD, Borden WB, Bravata DM, Dai S, Ford ES, Fox CS, Franco S, Fullerton HJ, Gillespie C, Hailpern SM, Heit JA, Howard VJ, Huffman MD, Kissela BM, Kittner SJ, Lackland DT, Lichtman JH, Lisabeth LD, Magid D, Marcus GM, Marelli A, Matchar DB, McGuire DK, Mohler ER, Moy CS, Mussolino ME, Nichol G, Paynter NP, Schreiner PJ, Sorlie PD, Stein J, Turan TN, Virani SS, Wong ND, Woo D, Turner MB. American Heart Association Statistics C, Stroke Statistics S. Heart disease and stroke statistics--2013 update: a report from the American Heart Association. Circulation. 2013; 127:e6–e245. [PubMed: 23239837]

Grundy SM, Cleeman JI, Daniels SR, Donato KA, Eckel RH, Franklin BA, Gordon DJ, Krauss RM, Savage PJ, Smith SC Jr, Spertus JA, Costa F. American Heart A, National Heart L, Blood I. Diagnosis and management of the metabolic syndrome: an American Heart Association/National Heart, Lung, and Blood Institute Scientific Statement. Circulation. 2005; 112:2735–2752. [PubMed: 16157765]

Karatsoreos IN, Bhagat S, Bloss EB, Morrison JH, McEwen BS. Disruption of circadian clocks has ramifications for metabolism, brain, and behavior. Proc Natl Acad Sci U S A. 2011; 108:1657–1662. [PubMed: 21220317]

Karlsson B, Knutsson A, Lindahl B. Is there an association between shift work and having a metabolic syndrome? Results from a population based study of 27,485 people. Occup Environ Med. 2001; 58:747–752. [PubMed: 11600731]

Kim MJ, Son KH, Park HY, Choi DJ, Yoon CH, Lee HY, Cho EY, Cho MC. Association between shift work and obesity among female nurses: Korean Nurses' Survey. BMC public health. 2013; 13:1204. [PubMed: 24354395]

Kirsh V, Cotterchio M, McGlynn N. 0219 The association between shift work and obesity in Canada: A cross-sectional study using a novel exposure assessment tool. Occup Environ Med. 2014; 71(Suppl 1):A88.

Knutsson A, Kempe A. Shift work and diabetes - A systematic review. Chronobiol Int. 2014:1–6.

Leproult R, Holmback U, Van Cauter E. Circadian misalignment augments markers of insulin resistance and inflammation, independently of sleep loss. Diabetes. 2014; 63:1860–1869. [PubMed: 24458353]

Lieu SJ, Curhan GC, Schernhammer ES, Forman JP. Rotating night shift work and disparate hypertension risk in African-Americans. J Hypertens. 2012; 30:61–66. [PubMed: 22134389]

Lim AS, Kowgier M, Yu L, Buchman AS, Bennett DA. Sleep Fragmentation and the Risk of Incident Alzheimer's Disease and Cognitive Decline in Older Persons. Sleep. 2013; 36:1027–1032. [PubMed: 23814339]

Lim AS, Srivastava GP, Yu L, Chibnik LB, Xu J, Buchman AS, Schneider JA, Myers AJ, Bennett DA, De Jager PL. 24-hour rhythms of DNA methylation and their relation with rhythms of RNA expression in the human dorsolateral prefrontal cortex. PLoS genetics. 2014; 10:e1004792. [PubMed: 25375876]

Lim AS, Yu L, Costa MD, Buchman AS, Bennett DA, Leurgans SE, Saper CB. Quantification of the fragmentation of rest-activity patterns in elderly individuals using a state transition analysis. Sleep. 2011; 34:1569–1581. [PubMed: 22043128]

Lim AS, Yu L, Costa MD, Leurgans SE, Buchman AS, Bennett DA, Saper CB. Increased fragmentation of rest-activity patterns is associated with a characteristic pattern of cognitive impairment in older individuals. Sleep. 2012; 35:633–640. [PubMed: 22547889]

Luik AI, Zuurbier LA, Hofman A, Van Someren EJ, Tiemeier H. Stability and fragmentation of the activity rhythm across the sleep-wake cycle: the importance of age, lifestyle, and mental health. Chronobiol Int. 2013; 30:1223–1230. [PubMed: 23971909]

Marcheva B, Ramsey KM, Buhr ED, Kobayashi Y, Su H, Ko CH, Ivanova G, Omura C, Mo S, Vitaterna MH, Lopez JP, Philipson LH, Bradfield CA, Crosby SD, JeBailey L, Wang X, Takahashi JS, Bass J. Disruption of the clock components CLOCK and BMAL1 leads to hypoinsulinaemia and diabetes. Nature. 2010; 466:627–631. [PubMed: 20562852]

Marler MR, Gehrman P, Martin JL, Ancoli-Israel S. The sigmoidally transformed cosine curve: a mathematical model for circadian rhythms with symmetric non-sinusoidal shapes. Stat Med. 2006; 25:3893–3904. [PubMed: 16381069]

Monk TH, Buysse DJ. Exposure to shift work as a risk factor for diabetes. J Biol Rhythms. 2013; 28:356–359. [PubMed: 24132061]

Monk TH, Petrie SR, Hayes AJ, Kupfer DJ. Regularity of daily life in relation to personality, age, gender, sleep quality and circadian rhythms. J Sleep Res. 1994; 3:196–205. [PubMed: 10607126]

National Cholesterol Education Program Expert Panel on Detection E, Treatment of High Blood Cholesterol in A. Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. Circulation. 2002; 106:3143–3421. [PubMed: 12485966]

Nelson W, Tong YL, Lee JK, Halberg F. Methods for cosinor-rhythmometry. Chronobiologia. 1979; 6:305–323. [PubMed: 548245]

Niedhammer I, Lert F, Marne MJ. Prevalence of overweight and weight gain in relation to night work in a nurses' cohort. Int J Obes Relat Metab Disord. 1996; 20:625–633. [PubMed: 8817356]

Ohira T, Tanigawa T, Iso H, Odagiri Y, Takamiya T, Shimomitsu T, Hayano J, Shimamoto T. Effects of shift work on 24-hour ambulatory blood pressure and its variability among Japanese workers. Scandinavian journal of work, environment & health. 2000; 26:421–426.

Ohlander J, Keskin MC, Stork J, Radon K. 0170 Shift work and hypertension: prevalence and analysis of disease pathways in German car manufacturing workers. Occup Environ Med. 2014; 71(Suppl 1):A81.

Oishi M, Suwazono Y, Sakata K, Okubo Y, Harada H, Kobayashi E, Uetani M, Nogawa K. A longitudinal study on the relationship between shift work and the progression of hypertension in male Japanese workers. J Hypertens. 2005; 23:2173–2178. [PubMed: 16269958]

Pan A, Schernhammer ES, Sun Q, Hu FB. Rotating night shift work and risk of type 2 diabetes: two prospective cohort studies in women. PLoS Med. 2011; 8:e1001141. [PubMed: 22162955]

Paudel ML, Taylor BC, Ancoli-Israel S, Stone KL, Tranah G, Redline S, Barrett-Connor E, Stefanick ML, Ensrud KE. Rest/Activity rhythms and cardiovascular disease in older men. Chronobiol Int. 2011; 28:258–266. [PubMed: 21452921]

Portaluppi F, Smolensky MH, Touitou Y. Ethics and methods for biological rhythm research on animals and human beings. Chronobiol Int. 2010; 27:1911–1929. [PubMed: 20969531]

R Development Core Team. R: A language and environment for statistical computing. Vienne, Austria: R Foundation for Statistical Computing; 2008.

Scheer FA, Hilton MF, Mantzoros CS, Shea SA. Adverse metabolic and cardiovascular consequences of circadian misalignment. Proc Natl Acad Sci U S A. 2009; 106:4453–4458. [PubMed: 19255424]

Scheer FA, Hu K, Evoniuk H, Kelly EE, Malhotra A, Hilton MF, Shea SA. Impact of the human circadian system, exercise, and their interaction on cardiovascular function. Proc Natl Acad Sci U S A. 2010; 107:20541–20546. [PubMed: 21059915]

Scheer FA, Michelson AD, Frelinger AL 3rd, Evoniuk H, Kelly EE, McCarthy M, Doamekpor LA, Barnard MR, Shea SA. The human endogenous circadian system causes greatest platelet activation during the biological morning independent of behaviors. PLoS One. 2011; 6:e24549. [PubMed: 21931750]

Shi SQ, Ansari TS, McGuinness OP, Wasserman DH, Johnson CH. Circadian disruption leads to insulin resistance and obesity. Curr Biol. 2013; 23:372–381. [PubMed: 23434278]

Sokolove PG, Bushell WN. The chi square periodogram: its utility for analysis of circadian rhythms. J Theor Biol. 1978; 72:131–160. [PubMed: 566361]

Swaab DF, Van Someren EJ, Zhou JN, Hofman MA. Biological rhythms in the human life cycle and their relationship to functional changes in the suprachiasmatic nucleus. Prog Brain Res. 1996; 111:349–368. [PubMed: 8990925]

Turek FW, Joshu C, Kohsaka A, Lin E, Ivanova G, McDearmon E, Laposky A, Losee-Olson S, Easton A, Jensen DR, Eckel RH, Takahashi JS, Bass J. Obesity and metabolic syndrome in circadian Clock mutant mice. Science. 2005; 308:1043–1045. [PubMed: 15845877]

van Amelsvoort LG, Schouten EG, Kok FJ. Duration of shiftwork related to body mass index and waist to hip ratio. Int J Obes Relat Metab Disord. 1999; 23:973–978. [PubMed: 10490804]

van Someren EJ, Hagebeuk EE, Lijzenga C, Scheltens P, de Rooij SE, Jonker C, Pot AM, Mirmiran M, Swaab DF. Circadian rest-activity rhythm disturbances in Alzheimer's disease. Biol Psychiatry. 1996; 40:259–270. [PubMed: 8871772]

Van Someren EJ, Kessler A, Mirmiran M, Swaab DF. Indirect bright light improves circadian rest-activity rhythm disturbances in demented patients. Biol Psychiatry. 1997; 41:955–963. [PubMed: 9110101]

Van Someren EJ, Riemersma-Van Der Lek RF. Live to the rhythm, slave to the rhythm. Sleep Med Rev. 2007; 11:465–484. [PubMed: 18021942]

WHO Expert Committee on Physical Status: the Use and Interpretation of Anthropometry. Physical status : the use and interpretation of anthropometry : report of a WHO Expert Committee. Geneva: World Health Organization; 1995.

Witting W, Kwa IH, Eikelenboom P, Mirmiran M, Swaab DF. Alterations in the circadian rest-activity rhythm in aging and Alzheimer's disease. Biol Psychiatry. 1990; 27:563–572. [PubMed: 2322616]

Wyatt JK, Ritz-De Cecco A, Czeisler CA, Dijk DJ. Circadian temperature and melatonin rhythms, sleep, and neurobehavioral function in humans living on a 20-h day. Am J Physiol. 1999; 277:R1152–R1163. [PubMed: 10516257]

Yamasaki F, Schwartz JE, Gerber LM, Warren K, Pickering TG. Impact of shift work and race/ethnicity on the diurnal rhythm of blood pressure and catecholamines. Hypertension. 1998; 32:417–423. [PubMed: 9740605]

Yusuf S, Reddy S, Ounpuu S, Anand S. Global burden of cardiovascular diseases: part I: general considerations, the epidemiologic transition, risk factors, and impact of urbanization. Circulation. 2001; 104:2746–2753. [PubMed: 11723030]

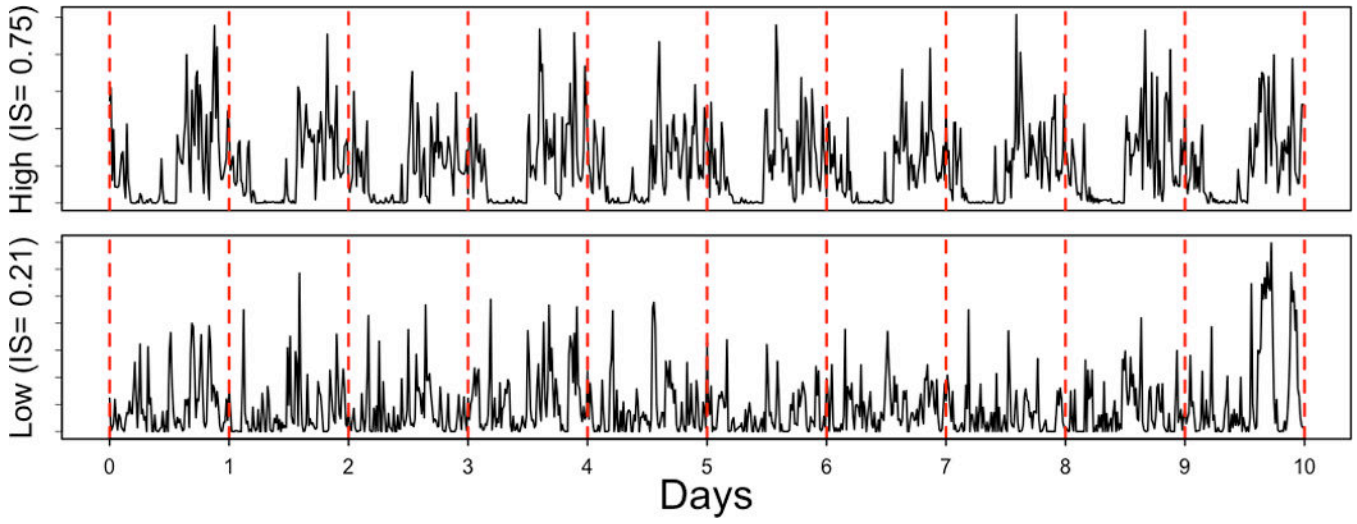

Figure 1. Representative Actigraphic Records

Individuals with high (top panel; interdaily stability 0.75) and low (bottom panel; interdaily stability 0.21) actigraphic rhythmicity but similar total daily activity. X-axis: time in days. Y-axis: activity counts.

Table 1

Characteristics of the Study Subjects (n=1137)

Characteristic	Mean (SD) or N (%)			p-value
	All (n=1137)	Without Metabolic Syndrome (n=905)	With Metabolic Syndrome (n=232)	
Age (years)	81.6 (7.5)	81.9 (7.5)	80.4 (7.3)	0.007
Female Sex	867 (76%)	207 (77%)	169 (73%)	0.20
Dementia	90 (8%)	69 (8%)	21 (9%)	0.56
Smoking	465 (42%)	375 (41%)	90 (39%)	0.44
Baseline Alcohol Consumption (g)	5.3 (12.1)	4.9 (13.0)	5.4 (11.8)	0.60
Body Mass Index (kg/m^2)	27.1 (5.2)	25.7 (4.2)	32.2 (5.5)	<0.001
Interdaily Stability	0.55 (0.13)	0.56 (0.13)	0.50 (0.14)	<0.001
Obesity	260 (23%)	96 (11%)	164 (71%)	<0.001
Hypertension	892 (78%)	664 (73%)	228 (98%)	<0.001
Diabetes	174 (15%)	42 (5%)	132 (57%)	<0.001
Dyslipidemia	613 (54%)	391 (43%)	222 (96%)	<0.001
Cardiovascular Disease	319 (28%)	223 (25%)	96 (41%)	<0.001
Stroke	125 (12%)	94 (10%)	31 (13%)	0.20
Coronary Artery Disease	131 (12%)	97 (11%)	34 (15%)	0.12
Peripheral Vascular Disease	133 (12%)	86 (10%)	47 (20%)	<0.001

TABLE 2

Associations between regularity of the activity rhythm and the metabolic syndrome (n=1137)

		Odds Ratio [95% CI] p-value of outcome associated with a 1SD increase in IS				
Model	**Covariates**	**Metabolic Syndrome**	**Obesity**	**Hypertension**	**Diabetes**	**Dyslipidemia**
A	Age, Sex	0.69 [0.60,0.80] 5.8e-07	0.73 [0.63,0.85] 2.5e-05	0.78 [0.66,0.91] 2.0e-03	0.76 [0.65,0.90] 9.3e-04	0.82 [0.72,0.92] 1.2e-03
B	A + Total Activity	0.75 [0.65,0.88] 3.5e-04	0.78 [0.66,0.91] 1.4e-03	0.80 [0.68,0.95] 1.1e-02	0.83 [0.70,0.98] 3.1e-02	0.85 [0.75,0.97] 1.6e-02
C	A + Total Rest	0.74 [0.63,0.87] 1.8e-04	0.79 [0.67,0.92] 3.0e-03	0.78 [0.66,0.93] 5.4e-03	0.83 [0.70,0.99] 3.5e-02	0.86 [0.75,0.98] 2.2e-02
F	A + IV	0.72 [0.61,0.85] 5e-05	0.76 [0.64,0.89] 7.4e-04	0.84 [0.71,0.99] 4.7e-02	0.81 [0.68,0.97] 1.9e-02	0.82 [0.72,0.94] 5.2e-03
G	A + kRA	0.70 [0.61,0.81] 2.2e-06	0.74 [0.64,0.86] 5.4e-05	0.79 [0.67,0.93] 4.1e-03	0.80 [0.68,0.94] 5.5e-03	0.83 [0.74,0.94] 3.9e-03
H	A + BMI	0.79 [0.67,0.94] 7.6e-03	NA	0.83 [0.70,0.98] 2.6e-02	0.81 [0.69,0.96] 1.5e-02	0.87 [0.76,0.99] 2.9e-02
I	A + CAD + Stroke + PVD	0.66 [0.56,0.77] 2.3e-07	0.70 [0.60,0.82] 1.0e-05	0.82 [0.69,0.97] 2.3e-02	0.75 [0.63,0.89] 9.5e-04	0.82 [0.72,0.94] 4.2e-03
J	A + Dementia	0.70 [0.60,0.81] 1.3e-06	0.71 [0.62,0.83] 8.3e-06	0.78 [0.66,0.91] 1.9e-03	0.82 [0.70,0.96] 1.3e-02	0.82 [0.73,0.93] 2e-03
K	A + Smoking + Alcohol	0.70 [0.60,0.81] 1.1e-06	0.73 [0.63,0.85] 2.8e-05	0.78 [0.67,0.92] 2.8e-03	0.79 [0.68,0.93] 3.9e-03	0.82 [0.72,0.93] 1.4e-03
L	A + All	0.70 [0.58,0.84] 1.5e-04	0.73 [0.60,0.88] 8.9e-04	0.80 [0.66,0.98] 3.2e-02	0.84 [0.69,1.03] 9.3e-02	0.85 [0.73,0.99] 3.6e-02

Abbreviations: OR Odds Ratio. CI confidence interval. SD standard deviation. IS interdaily stability, as calculated in the text. BMI body mass index. CAD coronary artery disease. PVD peripheral vascular disease. IV intradaily variability, as calculated in the text. kRA sleep fragmentation, as calculated in the text. Alcohol consumption measured in grams per week. Obesity, hypertension, diabetes, and dyslipidemia as defined in the text. Metabolic syndrome defined as 3 or more of obesity, hypertension, diabetes, or dyslipidemia.

TABLE 3

Association between regularity of the activity rhythm and continuous measures of body weight, blood pressure, glucose regulation, and dyslipidemia

		Estimate (SE) p-value on outcome associated with a 1SD increase in IS				
Model	**Covariates**	**BMI n=1137**	**sBP n=497**	**dBP n=497**	**HbA1C n=434**	**HDL n=665**
M	Age, Sex	−0.81 (0.15) 1.7e-07	−1.75 (0.89) 5.0e-02	−1.22 (0.51) 1.7e-02	−0.01 (0.02) 6.6e-01	3.03 (0.72) 2.9e-05
N	L + Total Activity	−0.66 (0.16) 5.2e-05	−1.83 (0.94) 5.3e-02	−1.14 (0.54) 3.6e-02	−0.01 (0.02) 6.4e-01	2.45 (0.76) 1.3e-03
O	L + Total Rest	−0.57 (0.17) 7.1e-04	−1.98 (1.00) 4.8e-02	−0.98 (0.57) 8.9e-02	−0.01 (0.02) 5.6e-01	2.27 (0.79) 4e-03
P	L + IV	−0.69 (0.17) 6.2e-05	−2.21 (1.04) 3.4e-02	−1.47 (0.61) 1.6e-02	−0.02 (0.02) 4.3e-01	2.88 (0.80) 3.7e-04
Q	L + kRA	−0.78 (0.15) 5.1e-07	−1.58 (0.90) 7.9e-02	−1.08 (0.52) 3.6e-02	−0.01 (0.02) 6.7e-01	2.92 (0.73) 7.2e-05
R	L + BMI	NA	−1.26 (0.90) 1.6e-01	−0.85 (0.51) 9.8e-02	0.00 (0.02) 9.6e-01	2.03.0 (0.73) 5.7e-03
S	L + CAD + Stroke + PVD	−0.86 (0.16) 1.7e-07	−1.08 (0.97) 2.7e-01	−0.88 (0.57) 1.2e-01	−0.03 (0.02) 2.8e-01	2.45 (0.74) 1.1e-03
T	L + Dementia	−0.86 (0.16) 4.4e-08	−1.68 (0.90) 6.3e-02	−1.12 (0.52) 3.1e-02	−0.00 (0.02) 8.6e-01	2.76 (0.74) 1.9e-04
U	L + Smoking + Alcohol	−0.80 (0.15) 2.9e-07	−1.51 (0.89) 9.0e-02	−1.07 (0.51) 3.2e-02	−0.01 (0.02) 7.5e-01	2.68 (0.72) 2.1e-04

Abbreviations: SE Standard Error. IS interdaily stability, as calculated in the text. IV intradaily variability, as calculated in the text. kRA sleep fragmentation as calculated in the text. Alcohol consumption measured in grams per week. BMI body mass index expressed as kg/m^2. CAD coronary artery disease. CHF congestive heart failure. sBP systolic blood pressure expressed as millimeters of mercury. dBP diastolic blood pressure expressed as millimeters of mercury. HbA1C the percentage of glycated hemoglobin. HDL high density lipoprotein expressed as mg/dL.

Table 4

Association between regularity of the activity rhythm, presence of the metabolic syndrome, and odds of having cardiovascular disease (n=1137)

Model	Predictors	Odds Ratio [95% CI] p-value of CVD Associated with 1SD change in IS	Odds Ratio [95% CI] p-value of CVD associated with presence of metabolic syndrome
V	IS	0.83 [0.73,0.95] 5.7e-03	NA
W	Metabolic Syndrome	NA	2.49 [1.81,3.41] 1.6e-08
X	IS and Metabolic Syndrome	0.88 [0.77,1.00] 5.5e-02	2.37 [1.72,3.26] 1.2e-07

Abbreviations: CVD cardiovascular disease; SE standard error; SD standard deviation; IS interdaily stability. All models adjusted for age and sex.