#### ORIGINAL ARTICLE

# Obesity Science and Practice V

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# Inconsistent social rhythms are associated with abdominal adiposity after involuntary job loss: An observational study

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#### **Funding information**

National Heart, Lung, and Blood Institute, Grant/Award Number: #1R01HL117995-01A1

## Abstract

**Objective:** Unemployment is an established risk factor for obesity. However, few studies have examined obesity-related health behavior after involuntary job loss specifically. Job loss confers a disruption in daily time structure that could lead to negative metabolic and psychological outcomes through chronobiological mechanisms. This study examines whether individuals with unstable social rhythms after involuntary job loss present with higher abdominal adiposity than individuals with more consistent social rhythms and whether this relationship varies as a function of depressive symptoms.

**Methods:** Cross-sectional baseline data (*n* = 191) from the ongoing Assessing Daily Activity Patterns in occupational Transitions (ADAPT) study were analyzed using linear regression techniques. Participants completed the Social Rhythm Metric-17 (SRM) daily over 2 weeks. They also completed the Beck Depression Inventory II (BDI-II) and participated in standardized waist circumference measurements (cm). **Results:** A significant interaction emerged between SRM and BDI-II demonstrating that less consistent social rhythms were associated with larger waist circumference at lower levels of depressive symptoms. Additional exploratory analyses demonstrated a positive association between the number of daily activities performed alone and waist circumference when controlling for symptoms of depression.

**Conclusion:** These findings are the first to demonstrate a relationship between social rhythm stability and abdominal adiposity in adults who have recently, involuntarily lost their jobs. Results highlight the moderating role of depressive symptoms on daily routine in studies of metabolic health. Future prospective analysis is necessary to examine causal pathways.

#### KEYWORDS

abdominal obesity, depression, social rhythm, unemployment, waist circumference

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# 1 | INTRODUCTION

The prevalence of obesity continues to rise in the United States, with 42.4% of adults, or 137.8 million people affected.<sup>1</sup> In particular, abdominal adiposity, one type of classification of overweight and obesity measured via waist circumference, is a powerful predictor of morbidity and mortality from chronic diseases.<sup>2,3</sup> Specifically, an excess accumulation of visceral or abdominal adipose tissue heightens cardiovascular and metabolic risk and related chronic disease<sup>3-5</sup> Abdominal adiposity correlates with risk factors including high blood pressure and adverse cholesterol and glucose profiles.<sup>6,7</sup> Obesity-related conditions are preventable, yet are one of the leading causes of premature death.<sup>1</sup>

Social risk factors, like unemployment, are associated with a major risk of obesity.<sup>8-10</sup> In 2007–2009, more than 15 million people experienced unemployment as part of the Great Recession.<sup>11</sup> The declines in employment and economic security exacerbated health problems in our nation and led to decreased self-reported physical and mental health, including increases in obesity, smoking, psychological distress, and suicide.<sup>8,9</sup> The negative impact of job loss on obesity is thought to operate through multiple causal pathways. Job loss leads to financial strain, which can contribute to food insecurity<sup>12</sup> and reduced access to healthy food options that are often more expensive.<sup>13</sup> Financial strain is also a chronic stressor, and chronic stress contributes to a preference for high-caloric foods<sup>14</sup> and fewer health-based decisions when eating.<sup>15</sup> In addition to chronic stress, job loss is a stressful life event; stressful life events lead to later weight gain.<sup>10,16</sup> Stressful life events also lead to reductions in health behaviors, such as physical activity.<sup>17</sup> To our knowledge, few studies have examined how the loss of time structure after job loss might negatively impact health.

Beyond providing financial solvency, employment establishes a behavioral routine that promotes multiple functions for the individual.<sup>18</sup> Employment imposes time structure to the day, increases social contact, assigns personal and collective meaning, and requires regular activity.<sup>18</sup> For this reason, employment is an important component of an individual's social rhythm, or pattern of habitual, daily behaviors. Social rhythms refer to the variability in habitual daily routine and are likely entrained through light exposure, the major environmental cue (or *zeitgeber*) closely linked to the expression and timing of circadian rhythms.<sup>19</sup>

Ehlers, Frank, and Kupfer<sup>20</sup> argue that through a destabilizing event or loss, such as involuntary unemployment, the lack of social *zeitgebers* leads to an unstable social rhythm, which, in turn, destabilizes the biological system. This destabilization can lead to a depressive state in vulnerable individuals. Subsequent research has supported this concept, identifying social rhythm disruption as a trigger to depressive episodes.<sup>21</sup> Furthermore, circadian rhythm disruptions are a typical marker of psychiatric illness,<sup>22</sup> and depressed individuals demonstrate less consistent social rhythms than their healthy controls.<sup>19,23</sup>

To our knowledge, no studies have examined social or circadian rhythm disruption among individuals with recent job loss, though Obesity Science and Practice \_\_\_\_\_\_WILEY

research works have shown that the misalignment of social and circadian clocks predisposes individuals to adverse health consequences. Research conducted on the discrepancy between social and biological time, termed "social jetlag," has identified the health risks derived from this disruption.<sup>24</sup> Social jetlag can be described by how one's social schedule (like work or school) deviates from their personal timing preference of sleep and activity.<sup>25</sup> This instability reduces insulin sensitivity<sup>26</sup> and is associated with adverse changes in cortisol levels.<sup>27</sup> Studies have also demonstrated that social jetlag promotes greater adiposity,<sup>26,28</sup> including a higher body mass index (BMI) and waist circumference,<sup>28,29</sup> with individuals more likely to meet the criteria for metabolic syndrome.<sup>28</sup>

Although the constructs of social jetlag and social rhythms tend to overlap in the literature, they are conceptually distinct in terms of timeframe. Social rhythms refer to day-to-day variability in habitual, daily behaviors or routines.<sup>20</sup> Social jetlag typically refers to variability in rise time from weekend to weekday.<sup>25</sup> Theoretically, individuals with higher levels of social jetlag would have more unstable social rhythms, as both constructs are characterized by highly variable wake and sleep times<sup>25</sup> that could represent a misalignment in circadian and social timing. However, research has not directly compared social jetlag and social rhythms, potentially due to the fact that unstable social rhythms and social jetlag occur in the natural environment over the course of weeks, rather than days. As a result, it is difficult to test changes in the timing of the circadian clock.

However, experimental studies utilizing the gold-standard forced desynchrony protocols have found support for the relationship between circadian misalignment and negative health outcomes. Temporary phase shifts are associated with a reduction of insulin sensitivity and increase in inflammation,<sup>30</sup> an increase in glucose, an increase in mean arterial pressure, decreased leptin, and adverse changes in cortisol levels.<sup>31</sup> The misalignment of the circadian and social rhythms could be a risk factor in developing depression.<sup>32</sup> Individuals who have depression also show higher levels of biological and social misalignment.<sup>33</sup>

Depression is also an important consideration in obesity. Both cross-sectional and longitudinal research support a bidirectional relationship between the two health conditions.<sup>34-36</sup> A meta-analysis of longitudinal studies found that depression increases the risk of becoming obese by 58%, and obesity increases the risk of depression by 55%.<sup>36</sup> Depression is also associated with abdominal obesity,<sup>37</sup> although the temporal ordering of this relationship is unclear due to a paucity of research examining depression and waist circumference over time. One cross-sectional study reported that abdominal fat distribution accounts for the majority of the relationship between depression and BMI,<sup>38</sup> suggesting that central obesity may have unique linkages to depression.

Taken together, these data suggest that unstable or inconsistent social rhythms may disrupt the expression of circadian rhythms, contributing to the risk of obesity and depression. Using crosssectional data from the Assessing Daily Activity Patterns through occupational Transitions (ADAPT) study, the current analysis sought to identify whether depressive symptoms moderate the relationship WILEY\_ Obesity Science and Practice

between social rhythm disruption and waist circumference in adults who recently experienced involuntary job loss. Because depression has been previously associated with both social rhythm instability<sup>19</sup> and higher waist circumference,<sup>35</sup> it was hypothesized that inconsistent social rhythms would be associated with higher levels of abdominal adiposity in individuals with increased reports of depressive symptoms as compared to individuals with fewer symptoms.

# 2 | METHODS

Data for this cross-sectional analysis were collected as part of the ADAPT study, an 18-month closed cohort study previously described.<sup>39</sup> Study participants were recruited through the Arizona Department of Economic Security after requesting application material for unemployment insurance. Individuals were eligible to participate if they were 25–60 years old and experienced involuntary job loss (laid-off or terminated) from full-time employment within the last 90 days. All data for this analysis were extracted from the baseline visit. This project was approved by the University of Arizona Human Subjects Protection Program and procedures have been performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

#### 2.1 | Participants

A total of 446 participants were recruited and screened for exclusion criteria to yield the final baseline sample of n = 191 participants who were eligible for the initial visit.<sup>39</sup> All participants eligible for the parent project were included in this analysis. To ensure changes in social rhythms associated with job loss could be detected, participants must have been employed at their previous, permanent job for a minimum of 6 months, working at least 30 h a week.

Participants were further screened and excluded for recent participation in treatments likely to influence weight or energy balance-related behaviors, including weight loss surgery and weight loss programs. Similarly, participants were disqualified for particular variables likely to impact sleep, detailed in Haynes et al.<sup>39</sup> Other exclusion criteria included taking part in shift work in the last month, meeting the criteria for substance abuse or dependence, or taking narcotics for sleep and pain in the previous 6 weeks. The top reasons for exclusion were employment criteria (e.g., being offered a new job >5 h per week, greater than 90 days since job loss; n = 100) and sleep disorder criteria (e.g., positive objective screen for sleep disordered breathing, current sleep apnea; n = 93). See Table 1 for participant demographics.

# 2.2 | Procedure

Participants were recruited from 2015–2018 as previously described<sup>39</sup> after being identified through unemployment claims filed

TABLE 1	Participant characteristics ( $n = 191$ )	
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Variable	N (%)	M (SD)
Sex		
Male	74 (39)	
Female	117 (61)	
Ethnicity		
Hispanic/Latino	63 (33)	
Not Hispanic/Latino	128 (67)	
Age, years		40.40 (9.90)
Days since job loss		41.65 (19.72)
Beck Depression Inventory		12.01 (9.99)
Waist circumference, cm		
Male		102.26 (17.66)
Female		99.90 (21.06)

through the Arizona Department of Economic Security Unemployment Insurance office. At the screening visit, staff informed participants about the study and received written informed consent. After the consenting process, inclusion criteria were assessed, including demographics and information about the previous job. Within the next 2 weeks, participants returned for the initial baseline visit where they completed multiple questionnaires and interviews relevant to study aims. Relevant to this analysis, the participants completed the Beck Depression Inventory (BDI-II)<sup>40</sup> and participated in body measurements, including assessment of waist circumference. At the end of the visit, participants were given a smart tablet with instructions to complete the Social Rhythm Metric (SRM)<sup>41</sup> each evening for the next 2 weeks. The participant flow diagram was reported previously.<sup>42</sup>

# 2.3 | Measures

#### 2.3.1 | Demographics

Study staff administered a demographic interview with questions assessing age, sex, ethnicity, race and time since job loss.

#### 2.3.2 | Beck Depression Inventory II

To assess for depression symptoms, the valid and reliable BDI-II<sup>40</sup> was administered. This is a 21 item, self-report instrument that measures the severity of both cognitive and somatic symptoms of depression. Internal consistency for the current sample was excellent, Cronbach's  $\alpha = 0.93$ . There were nine total missing values (0.25%) across four cases on the BDI, and no variables had 5% or more missing values. Multiple imputation (n = 5 datasets) was employed at the item-level to yield a pooled estimate of total BDI score.

## 2.3.3 | Social rhythms

The SRM was used to measure habitual daily behaviors and interactions. This is a valid<sup>43</sup> and reliable<sup>41</sup> self-report daily diary that measures the frequency and consistency of 15 activities. Aspects of daily behavior captured include timing of the first interpersonal interaction, meals, and leaving and returning home. The SRM yields two discrete indices that measure the following separate constructs 1: the SRM Index (SRM-I), a measure of stability or consistency of daily routine (higher scores = more stable), and<sup>2</sup> the Activity Level Index (ALI), a weekly count of performed activities.<sup>41</sup> A number of secondary indices can be computed from the ALI, including a count of the number of activities performed (a) alone (ALI-alone), (b) with others actively involved (ALI-active), or (c) with others just present (ALI-present).

The SRM index and ALI were considered missing if participants completed less than 4 days of the SRM (n = 5 cases missing for ALI; n = 6 cases missing for SRM). List-wise deletion was chosen on the basis of these independent variables, given the overall low level of missingness (3%) and lack of information about the total number of time-based items required to reliably compute the proposed indices.

# 2.3.4 | Waist circumference

Waist circumference (cm) was the measure of central adiposity. It was collected by trained staff using a Gulick II Tape Measure. As part of the standardized study protocol, participants stood in front of a mirror during waist measurement in order for staff to confirm the tape measure was level across the front and back of the waist prior to measurement.<sup>44</sup> Two separate waist measurements were taken at each assessment. If the first and second measurement differed by >0.05 cm, then a third measurement was taken. The average of the two measurements closest to each other were recorded for the outcome scores. Central obesity was chosen as the primary outcome as it is a stronger risk factor than BMI for cardiovascular disease, type 2 diabetes mellitus, and mortality.<sup>3,4</sup>

#### 2.4 | Statistical analysis

Analyses were conducted using the IBM SPSS Statistics version 26. Preliminary descriptive analyses were conducted to describe participant characteristics. Consistent with the common cause method of covariate selection,<sup>45</sup> analysis of variance or bivariate correlations were employed to test associations between theoretically informed demographic characteristics and the main variables of interest. The following demographic variables were assessed given prior documented associations with either social rhythm,<sup>46</sup> depression,<sup>47</sup> or waist circumference<sup>48</sup>: age, gender, race, ethnicity, and days since job loss. Demographic variables were explored and included as covariates in the main analyses if they were significantly associated with the outcome, waist circumference, and the independent variable, **Obesity Science and Practice** 

| 211

WILEY

each relevant social rhythm index (SRM-I or ALI). All independent variables (BDI and SRM variables) were mean centered to facilitate interpretation.<sup>49</sup>

For the main analyses, hierarchical linear regression was employed to test the effect of depressive symptoms on the relationship between the relevant SRM-I or ALI and abdominal adiposity. Initially, separate models were constructed that included statistically significant covariates in univariate analysis, the independent variable (either SRM-I or ALI), and the moderator (BDI); further, models were then evaluated that included the interaction between SRM and BDI. Probing of interactions was conducted using the Hayes PROCESS command v3.4 employing visualization and the Johnson-Neyman technique.<sup>49</sup> These procedures were repeated for follow-up, exploratory analyses examining the effect of each ALI subgroup on abdominal adiposity (activities performed: alone, with others just present, and with others actively involved). These analyses were conducted to inform future hypothesis testing; therefore, Bonferroni correction was not employed.<sup>50</sup>

# 3 | RESULTS

A total of 24 preliminary comparisons were conducted to assess covariates; 1 comparison would be expected to be statistically significant by chance at the level of  $\alpha = 0.05$ . One comparison emerged as significant: Hispanic ethnicity (1 = Hispanic; 0 = Other) was associated with a higher waist circumference, *F*(1, 190) = 7.52, p < 0.01. Hispanic ethnicity was not associated with any of the SRM indices. Therefore, the models remain unadjusted as recommended by the common cause method of covariate selection.<sup>45</sup> See Table 1 for participant demographics.

### 3.1 | Main analyses

The results from the main analyses are reported in Table 2.

A significant interaction between SRM and BDI score was found when predicting waist circumference (see Figure 1).

The interaction was decomposed by simple slopes analyses examining the centered SRM variable at +1 and -1 SD above and below the mean centered BDI score. The SRM was negatively associated with waist circumference, B = -5.53, SE = 2.24, t = -2.46, p < 0.05 (-9.95, -1.10, 95% confidence interval [CI]), only at lower levels of BDI (-1 SD below the mean score); a trend was observed at mean levels of BDI, B = -3.18, SE = 1.65, t = -1.84, p = 0.07 (-6.29, 0.21, 95% CI). No relationship was observed between SRM and waist circumference at higher levels of BDI (+1 SD above the mean score). Results from the Johnson-Neyman technique identified that the conditional effect of SRM on waist circumference is statistically significant at the 0.05 level when BDI is less than or equal to -3.95 points below the mean (or a raw score of 8.06 or less on the BDI). Approximately 44.86% of cases are within this region.

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				95% CI				
Variable	В	SE	t	LL	UL	ΔF	df	ΔR <sup>2</sup>
Model 1						4.26**	3, 181	0.07
SRM index	-1.91	1.64	-1.16	-5.15	1.34			
BDI	0.42	0.15	2.73**	0.12	0.73			
SRM index $\times$ BDI	0.36	0.18	1.99*	0.00	0.71	3.94*	1, 181	0.02
Model 2						4.30*	2, 183	0.05
ALI	-0.14	0.09	-1.46	-0.32	0.05			
BDI	0.32	0.15	2.20*	0.03	0.61			
Model 3						6.96**	2, 183	0.07
ALI-alone	-0.22	0.08	-2.69**	-0.38	-0.06			
BDI	0.34	0.14	2.42*	0.06	0.62			
Model 4						3.62*	3, 182	0.06
ALI-present	0.05	0.17	0.30	-0.29	0.39			
BDI	0.35	0.14	2.43*	0.07	0.63			
$\textbf{ALI-present} \times \textbf{BDI}$	-0.03	0.02	$-1.90^{t}$	-0.06	0.00	3.62 <sup>t</sup>	1, 182	0.02
Model 5						4.10*	2, 183	0.04
ALI-active	0.12	0.09	1.31	-0.06	0.31			
BDI	0.38	0.14	2.66**	0.10	0.66			

TABLE 2 Linear regression analyses examining the relationships between SRM Indices, BDI scores, and waist circumference

Notes: Main effects models are reported in the absence of a statistically significant interaction term. All BDI and SRM indices were mean centered. n = 186 for ALI analyses; n = 185 for SRM index analyses.

Abbreviations: ALI, activity level index; BDI, Beck Depression Inventory; CI, confidence interval; LL, lower limit; SRM, Social Rhythm Metric; UL, upper limit.

p < 0.10; p < 0.05; p < 0.01; p < 0.01.

The interaction between ALI and BDI was not significant. After removing the interaction term from the model, a main effect was found only for the BDI score indicating that overall higher levels of depressive symptoms were associated with higher waist circumference (see Figure 2). A similar pattern of results was found when substituting the ALI score with the ALI-active, with only a main effect BDI score.

For the exploratory analyses, the global ALI score was substituted with the ALI-alone index. The interaction was not significant, but main effects emerged for both ALI-alone and BDI score, indicating that higher levels of depressive symptoms and lower numbers of activities performed alone were each significantly associated with higher waist circumference. A trend emerged for the interaction between ALI-present and BDI term. The interaction was decomposed by simple slopes analyses examining the centered ALI-present variable at +1 and -1 SD above and below the mean centered BDI score. Results demonstrated that ALI-present had a weak, negative relationship with waist circumference, B = -10.16, SE = 0.20, t = 1.75, p = 0.08 (-0.04, 0.73, 95% Cl), only at lower levels of BDI (-1 SD below the mean score). No relationship was observed between ALI-present and waist circumference at the mean or higher levels of BDI (+1 SD above the mean score). With the

interaction term in the model, only a main effect for BDI on waist circumference remained.

#### DISCUSSION 4

To our knowledge, this study is one of the first to examine the relationship between social rhythms, depressive symptoms, and abdominal adiposity in a group of individuals whose schedules were unconstrained by full-time employment. Results suggest that unemployed individuals with more consistent daily routines had lower levels of abdominal adiposity, but only for those with minimal symptoms of depression. Conversely, social rhythm consistency was not associated with waist circumference in individuals experiencing above-average levels of depressive symptoms. Although depressive symptoms moderated the relationship between social rhythms and obesity, the moderation effect was in an opposite direction than originally hypothesized. These findings provide more support for the key role of depression symptoms in studies of abdominal adiposity.

Interestingly, the frequency of daily activities was unrelated to waist circumference. Activities on the SRM are behaviors that anchor the timing of the individual's daily routine<sup>43</sup>; they do not necessarily





FIGURE 2 Activity Level Index (ALI) Scores  $\times$  Beck Depression Inventory (BDI) interaction predicting waist circumference, cm (n = 185)

require energy expenditure (e.g., eat dinner, go to bed). Therefore, results demonstrating the importance of activity consistency, rather than frequency, can perhaps be explained by a conceptually overlapping areas in obesity research, self-regulation.

Insufficient self-regulation has been implicated in the development of each obesity<sup>51</sup> and depression.<sup>52</sup> To our knowledge, no studies have assessed social rhythms as a biobehavioral expression of self-regulation. However, both self-regulation and stable social rhythms may be associated with reward-motivated behavior. Reward system activation is critical to emotion, eating, and sleep.<sup>52,53</sup> Thus, individuals with hypersensitive reward pathways may be more likely to experience disrupted social rhythms or difficulties with selfregulation after stressful life events such as job loss,<sup>52,53</sup> leaving them at greater risk for obesity. Future research is necessary to evaluate the overlap between social rhythms and self-regulation including potential intermediary linkages with dietary dysregulation and depression.

Although there was no overall relationship between the number of activities and waist circumference, exploratory analyses demonstrated that a higher number of activities performed alone was associated with a greater waist circumference. The combination of activities performed with others present and actively involved appears to be driving this effect, since the frequency of activities involving active participation with others did not appear to uniquely predict waist circumference. These findings are consistent with previous research showing an important effect of socializing on energy balance, behaviors, and mood. One study<sup>54</sup> found that synchronizing solitary meals increases life satisfaction, while eating alone did not. Other studies have shown that individuals are more likely to exercise if others are involved<sup>55</sup> and that participants with more consistent social rhythms characterized by activities with others actively involved are less likely to be depressed.<sup>23</sup> Therefore, future prospective analysis is necessary to assess whether both social rhythm consistency and the frequency of activities performed with others

WILEY\_ Obesity Science and Practice

might mediate the relationship between depression and waist circumference.

This study supports the necessity of future work examining whether daily, consistent social rhythms could be important consideration in obesity prevention among nondepressed individuals who have suffered involuntary job loss. In this study, social rhythm consistency was less relevant for depressed individuals. One interpretation of these findings is that individuals experiencing higher levels of depressive symptoms have either inconsistent routines or consistent routines with fewer activities. The relationship between the ALI and BDI was not examined in the current study; all variables were centered and variance influence factors were acceptable, reducing concerns about multicollinearity for the main analyses. However, research has shown that depression is associated with a lower ALI<sup>19</sup> To test this question, future research is necessary examining the interaction between both the content and variability of routine.

Strengths of the study include daily assessment of social rhythm and assessment of objective measures of abdominal adiposity, one of the best markers for insulin sensitivity and health risk in middle age individuals.<sup>3,56</sup> A primary limitation of the study is the cross-sectional design. Interpretations regarding social rhythms and obesity may be reciprocal or reversed. Future prospective analyses are necessary to test directionality. Also, future work is necessary to examine whether these findings generalize to other groups who experience abrupt changes in social rhythms; examples may include children during summer break, veterans returning from deployment, or older adults who retire. Finally, there are a number of other factors beyond daily routine that may contribute to or prevent abdominal adiposity, including workplace wellness intervention for obesity,<sup>57</sup> but those variables are beyond the scope of this current investigation. Despite these limitations, these findings are the first to demonstrate a relationship between social rhythm stability and abdominal adiposity. Findings from this study are highly relevant to public health issues associated with job loss and economic recession. Overall results from this study indicate that depressive symptoms and the consistency of social rhythms, two modifiable conditions, may be important factors to consider in future studies of obesity and stress.

### ACKNOWLEDGMENTS

This research was supported by the National Heart, Lung, and Blood Institute (#1R01HL117995-01A1; PI: Haynes). The research team gratefully thanks the study participants and acknowledges the contributions of Devan Gengler, Darlynn Rojo-Wissar, April Yingst, Efreim "Joe" Morales, and Jesi Post. All data requests should be submitted to the corresponding author for consideration. Access to anonymised data may be granted following review.

#### CONFLICT OF INTERESTS

Gabriella Apolinar is employed by La Frontera Center–EMPACT. Stuart Quan is a consultant for Best Doctors, Jazz Pharmaceuticals, and Whispersom; a Committee Chair for the Scoring Manual Committee, American Academy of Sleep Medicine; and a taskforce member for the Hypopnea taskforce, American Academy of Sleep Medicine.

#### AUTHOR CONTRIBUTIONS

Patricia L. Haynes is the PI of ADAPT, the parent project; she conceived the idea and supervised this project. Patricia L. Haynes, Graciela E. Silva, David A. Glickenstein, Cynthia A. Thomson, and Stuart F. Quan contributed to research design. Candace Mayer, Ume Kobayashi, Gabriella R. Apolinar, Graciela E. Silva, David A. Glickenstein, and Stuart F. Quan assisted with data collection and processing. Patricia L. Haynes conducted statistical analyses. Patricia L. Haynes and Gabriella R. Apolinar drafted the manuscript. Patricia L. Haynes, Graciela E. Silva, David A. Glickenstein, Cynthia A. Thomson, and Stuart F. Quan interpreted results. Patricia L. Haynes, Ume Kobayashi, Gabriella R. Apolinar, and CM contributed to manuscript revision. All authors discussed the results and commented on the manuscript.

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**Obesity Science and Practice** 

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#### SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

How to cite this article: Haynes PL, Apolinar GR, Mayer C, et al. Inconsistent social rhythms are associated with abdominal adiposity after involuntary job loss: An observational study. *Obes Sci Pract.* 2021;7:208–216. <u>https://doi.org/10.1002/osp4.479</u>