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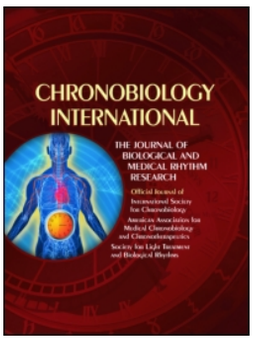

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ORIGINAL ARTICLE

Latent activity rhythm disturbance sub-groups and longitudinal change in depression symptoms among older men

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Activity rhythm disturbances and depression often co-occur among older adults. However, little is known about how activity rhythm disturbances themselves co-occur, or how disturbances to multiple aspects of the activity rhythm relate to depression over time. In this study, we performed a Latent Class Analysis to derive sub-groups of older men [total $n = 2933$, mean age = 76.28, standard deviation (SD) = 5.48] who shared similar patterns of activity rhythm disturbances (defined as extreme values of modeled activity rhythm parameters). We found eight sub-groups with distinct combinations of activity rhythm disturbances: one had all normative activity rhythm parameters (32.09%), one had only lower activity (10.06%), three had earlier activity (totaling 26.96%) and three had later activity (totaling 30.89%). Groups with similar timing were distinguished depending on whether the relative length of the active period was shorter and/or if the activity rhythm had lesser amplitude/robustness. We next examined whether the derived activity rhythm sub-groups were associated with different rates of change in depression symptom levels over an average of 5.5 (0.52 SD) follow-up years. The sub-group with lower activity only had faster increases in depressive symptoms over time (compared with the group with normative rhythm parameters), but this association was accounted for by adjustments for concurrently assessed health status covariates. Independent of these covariates, we found that four activity rhythm disturbance sub-groups experienced faster depressive symptom increases (compared with the normative sub-group): These included all three sub-groups that had later activity timing and one sub-group that had earlier activity timing plus a shorter active period and a dampened rhythm. Low activity rhythm height/robustness with normal timing therefore may mark depression risk that is attributable to co-occurring disease processes; in contrast, having late or combined early/compressed/dampened activity rhythms may independently contribute to depression symptom development. Our findings suggest that activity rhythm-related depression risk is heterogeneous, and may be detected when multiple aspects of rhythm timing are delayed or when early timing is accompanied by compressed/dampened activity rhythms. Future studies should consider how distinct combinations of altered activity rhythm timing and height/robustness develop and conjointly determine health risks. Further research is also needed to determine whether/how activity rhythms can be modified to improve depression outcomes.

Keywords: Actigraph, aging, circadian activity rhythm, depression, epidemiology, MrOS

INTRODUCTION

Activity rhythm disturbances are associated with depressed mood (Luik et al., 2013, 2015; Maglione et al., 2013; Robillard et al., 2014). Prior studies have identified particular activity rhythm characteristics (such as rhythm height, robustness or timing) linked to depression. However, like disease (Marengoni et al., 2009), activity rhythm disturbances may co-segregate in predictable and nuanced patterns. As of now it is unknown whether, and if so how, activity rhythm disturbances tend to co-occur. If patterns of co-

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occurring activity rhythm disturbances do exist, their impact on future depression has not yet been established.

To our knowledge, only one study to date has examined the longitudinal relationship between activity rhythms and future depression risk (Smagula et al., 2015), but this study was limited by a relatively short follow-up period (an average of 1.2 years) and by investigating activity rhythm characteristics separately. Therefore, the nature of activity rhythm-associated depression risk over longer time periods remains unclear, and it remains unknown whether specific combinations of activity rhythm disturbances synergistically elevate depression risk.

This study therefore first aimed to determine whether activity rhythm disturbances tend to co-segregate in specific patterns or combinations occurring within particular sub-groups. To do so, we applied a person-centered, data-driven approach [Latent Class Analysis (LCA)] to identify sub-groups that share similar patterns of co-occurring activity rhythm disturbances among a large sample of older men. Although this was a secondary data analysis, investigating activity rhythms in this group is important because both variability and disturbances are expected to be high. Aging is associated with increased activity rhythm fragmentation (Huang et al., 2002; Robillard et al., 2014) and compared with younger men and older women, circadian rhythms in behaviors and subjective ratings are most poorly entrained to the internal circadian rhythm (as referenced by rectal temperature) (Monk & Kupfer, 2000). To further clarify the relationship between activity rhythm disturbances and the course of depression among older men, we tested whether any of the data-derived sub-groups experienced greater depressive symptom increases over 5 years. This novel approach was designed to assess the patterns of co-occurring activity rhythm disturbances prevalent within a population-based sample of older men, and to assess whether specific activity rhythm disturbances, or their combinations, are associated with depression risk over time.

MATERIALS AND METHODS

Participants

The Osteoporotic Fractures in Men (MrOS) Sleep Study recruited 3135 participants at six study sites in the USA (Birmingham, AL; Minneapolis, MN; Palo Alto, CA; Monongahela Valley, PA; Portland, OR; and San Diego, CA) (Blank et al., 2005; Orwoll et al., 2005) between December 2003 and March 2005. The parent MrOS study included community dwelling men $\geq$65 years of age who could walk without assistance and were without bilateral hip replacements. Men were excluded from the Sleep Study if they regularly used overnight nocturnal oxygen therapy, positive pressure or oral appliances for treatment of sleep apnea ($n = 150$). Other reasons for non-participation in the Sleep Study were: death ($n = 349$), terminated study participation ($n = 39$), declined Sleep Study ($n = 1997$) or because MrOS Sleep Study recruitment goals had already been met ($n = 324$). All men provided written informed consent, and the study was approved by the Institutional Review Board at each site. For consistency with prior work (Paudel et al., 2011) and because 72 hours of recording is considered the minimum period for assessing sleep–wake patterns with actigraph (Ancoli-Israel et al., 2015; Littner et al., 2003), participants were required to have three or more, 24-hour periods of technically adequate actigraph data (excluded $n = 134$); therefore, the cross-sectional LCA was conducted with 3001 men [mean age = 76.35, standard deviation (SD) = 5.52]. To be included in the longitudinal analysis, participants were required to have complete outcome data from baseline and at least one other time point; 68 of the men failed to meet this criteria and were excluded from the longitudinal analysis (which included $n = 2933$ men).

Activity rhythm disturbances

Objective estimates of sleep/wake activity were obtained using the Octagonal Sleep Watch actigraphy, or SleepWatch-O, (Ambulatory Monitoring Inc, Ardsley, NY). Participants were asked to wear actigraphs on the non-dominant wrist for a minimum of five consecutive 24-hour periods except when bathing or during water sports. Movement was measured using a piezoelectric biomorph-ceramic cantilevered beam, which generates a voltage each time the actigraph is moved. These voltages are gathered continuously and stored in 1-minute epochs. Data collected in digital integration mode were used for this analysis. A five-parameter extended sigmoidally transformed cosine model with an antilogistic function was used to model activity data; this model fits activity rhythm data better than a standard cosine curve as humans typically exhibit a more ''squared'' activity rhythm (Marler et al., 2006).

Modeled parameters included measures of rhythm height, timing and robustness. For all activity rhythm parameters except the timing variables, we compared the lowest quartile with the others to represent deviations the sample's normative values (thus indicating activity rhythm disturbances). For timing parameters, the lowest and the highest quartiles were both compared with the others (in a single variable) to represent both phase advances and delays. Using quartiles to represent non-normative or disturbed activity rhythm parameters is consistent with previous work (Paudel et al., 2010; Smagula et al., 2015; Tranah et al., 2010, 2011) and, in the context of LCA, is designed to identify sub-groups with specific patterns of activity rhythm parameters outside the normative range (disturbances).

Rhythm height parameters were amplitude (peak-nadir difference) and mesor (middle of the fitted curve). To assess whether low rhythm height is a consequence of activity levels overall, rather than relative peak-nadir differences, standardized amplitude was computed (as

amplitude divided by mesor) with lower values indicating a dampened rhythm.

Rhythm timing measures were acrophase (time of day of peak activity level), up-mesor (time of day when activity passes up through mesor, approximating the time the participant ''gets going'' in the morning) and down-mesor (time of day when activity passes down through mesor, approximating the time of day the participant ''settles down'' for the night).

The extended cosine model also provides a measure known as the pseudo-*F* statistic which reflects of how well the modeled rhythm fits the observed data (Marler et al., 2006). Values indicate how robustly patterned activity is over the assessment period, with lower values indicating poorer model fit and suggesting an erratic and/or variable rhythm.

A parameter called alpha reflects the relative width of the activity peak compared with nadir; higher values indicate a relative narrowness of the active compared with rest period; the highest quartile was contrasted with the others to reflect a shorter activity period.

Outcome

The Geriatric Depression Scale-15 [GDS; (Sheikh & Yesavage, 1986)] was administered at baseline and three follow-up visits (conducted from March 2005 to May 2006, March 2007 to March 2009 and March 2009 to April 2011). Retention was high at the follow-up visits: of the men included in the longitudinal analysis, 99.5%, 90.1% and 81.2% contributed complete GDS data at these subsequent time points; in addition, note that 80.7% contributed GDS data at all four time points. The GDS contains 15 items with binary response options indicating whether the symptom was present or absent over the ''last week''. The GDS, a self-reported questionnaire, is a reliable and valid measure of depression among older adults. This version of the GDS indicates depression severity (compared with International Classification of Disease Version 10) and can therefore detect changes in depression over time (Almeida & Almeida, 1999). In this study, depression severity was examined over time as reflected by repeated total GDS scores (range 0–15).

Covariates

Demographics and lifestyle

Age, study site, race, weekly alcohol use, daily caffeine intake, educational attainment, smoking status and BMI (measured with a standard balance beam or digital scale and wall-mounted stadiometer) were examined as covariates. The Physical Activity Scale for the Elderly [a validated self-report physical activity measure (Schuit et al., 1997; Washburn et al., 1993)] was expressed as a continuous variable.

Mental health and cognitive impairment

Cognitive impairment was measured using the 3MS (Teng & Chui, 1987) which was expressed as a continuous variable. Anxiety symptoms were measured using the anxiety portion of the Goldberg Depression and Anxiety Scale (GDAS; Goldberg et al., 1988) as a continuous score reflecting symptom counts (range: 0–9).

Subjective sleep

The Pittsburgh Sleep Quality Index (PSQI) (Buysse et al., 1989) (range 0–21) was expressed continuously to reflect global sleep quality. The Epworth Sleepiness Scale (ESS) was also expressed as a continuous measure of excessive daytime sleepiness ranging from 0 to 24 (Johns, 1991).

Actigraph assessed sleep

ActionW-2 software (Ambulatory Monitoring Inc, Ardsley, NY) was used to score the actigraphy data; for scoring algorithms details see (Blackwell et al., 2005; Jean-Louis et al., 2001). This method produces reliable estimate of sleep–wake patterns (Ancoli-Israel et al., 2003; Pollak et al., 2001). Participants were also asked to keep a sleep log which was used to edit the actigraphy data. Inter-scorer reliability has been previously found to be high in sleep studies performed by the MrOS Sleep Study team (intra-class coefficient = 0.95) (Blackwell et al., 2005).

Actigraphy-derived sleep parameters (covariates) were: total sleep time (TST; hours per night spent sleeping in bed after ''lights off''), sleep latency (SL; amount of time until onset of sleep defined when participant achieved sleep for 20 continuous minutes in bed) and wake after sleep onset (WASO; minutes scored awake during the interval after sleep onset). Actigraphy measured sleep parameters were dichotomized to represent clinically significant disturbances: (1) short sleep <5 hours and long sleep >8 hours (contrasted in a single variable with 5–8 hour sleepers); (3) SL ≥ 60 minutes and (4) WASO ≥ 90 minutes.

Polysomnography-assessed sleep

In-home sleep studies were conducted using one night of unattended polysomnography (PSG) (Safiro, Compumedics Inc., Melbourne, Australia) as described previously (Mehra et al., 2007). Centrally trained and certified staff members performed home visits for setup of the sleep study units; methods were similar to those in the Sleep Health Heart Study (Redline et al., 1998). Polysomnography data quality was generally excellent, with a failure rate of $<4\%$ and $>70\%$ of studies graded as being of excellent or outstanding quality. The apnea hypopnea index (AHI) was computed as the average number of apneas and hypopneas per hour of recorded sleep using standard definitions of apneas and hypopnea (Quan et al., 1997). Rescoring studies over time indicates that inter- and intra- scorer reliability (ICC) for the AHI was high (ICC >0.95). The AHI was dichotomized at ≥ 30 to reflect severe sleep disordered breathing.

Sleep stages [rapid eye movement (REM), stages 1, 2 and slow wave sleep (N3 and N4 combined] were scored

using standard criteria (Rechtschaffen, 1968) and were expressed as the percentage of sleep time spent in these states. Also included was REM latency, which was defined as the number of minutes from sleep onset to the first REM period.

Instrumental Activity of Daily Living impairment

The number of five Instrumental Activity of Daily Living (IADL) impairments was expressed as a continuous variable. The five IADLs were: heavy housework, preparing own meals, shopping for groceries or clothing, walking two to three blocks and climbing 10 stairs (Fitti & Kovar, 1987; Pincus et al., 1983).

Chronic diseases and falls

Participants were asked if they had a fall in the past 12 months. They also reported whether they had ever received a physician diagnosis of peripheral vascular disease, osteoarthritis, rheumatoid arthritis, hypertension, stroke, angina, congestive heart failure, myocardial infarction, diabetes, chronic obstructive pulmonary disease, Parkinson's disease, renal disease, cataracts or liver disease.

Inflammatory markers

Serum was collected during morning clinic visits after an overnight fast. A natural log transformation was applied to normalize their distributions which were initially skewed. CRP was measured using the ELISA assay kit from ALPCO (CRP sensitive ELISA, ALPCO, Salem, NH). IL-6, TNF-α and IFN-γ were assayed using the Human ProInflammatory I 4-Plex Ultra-Sensitive Kit by MSD (catalog #K15009C-4). TNF-αsRII was measured with an ELISA from R&D Systems (Minneapolis, MN; catalog #DRT200). Inter-assay CVs for these markers have been published previously (Smagula et al., 2014a).

Medications

Participants were asked to bring all medications used within the last 30 days to the sleep examination. Medications were entered into an electronic database and matched to their ingredient(s) based on the Iowa Drug Information Service (IDIS) Drug Vocabulary (College of Pharmacy, University of Iowa, Iowa City, IA) (Pahor et al., 1994). Psychoactive medications (antidepressants, benzodiazepines and non-benzodiazepine non-barbiturate sedatives/hypnotics) were considered based on expected clinical relationships between these drugs and the primary predictors and outcomes. Other medications considered were NSAIDs and corticosteroids due to their relations with inflammatory markers and potentially the outcomes.

Psychosocial factors

During the visit occurring between March 2005 and May 2006 (approximately 1.2 years after the Sleep Visit), participants were asked whether, over the past 12 months, they had experienced any stressful event including ''Serious illness or accident of wife or partner'', ''Death of other close relative or close friend'', ''Separation from child, close friend, or other relative who participant depends on'', ''Loss of a pet'', ''Moved or changed in residence'', ''Serious financial trouble'' and ''Anything else important''. At this time, participants were also administered a questionnaire (Michael et al., 2001) providing measures of their social networks size and levels of social participation; responses to the individual questions from these measures were analyzed as covariates.

Statistical methods

Latent class analysis

LCA postulates the presence of an unmeasured categorical latent variable that directly causes an observed pattern of indicators (single variable items) within a given set. LCA assumes local independence, in other words conditional independence of the indicators given latent class assignment. In this analysis, indicators were dichotomous, except for timing variables which had three categories (i.e. early acrophase versus normative versus late acrophase representing the earliest quartile of activity peaks versus the middle two quartiles versus the latest quartile of activity peaks).

An add-in SAS procedure (PROC LCA) was utilized to conduct the LCA (Lanza et al., 2007). The number of latent groups was selected based on both interpretability and model fit statistics. The Bayesian Information Criterion (BIC) was used to compare models with a different number of latent classes (sub-groups). A smaller value is favored although BIC may indicate improvements in model fit when adding classes that do not reflect distinct or clinically relevant sub-groups. Therefore, although BIC was used to select the optimal number of latent classes, the number of latent groups was only increased when doing so captured a distinct and clinically relevant sub-group. Solutions with small latent classes (<5% of the sample) were rejected.

Growth curve modeling

The outcome was total GDS score reflecting overall depression symptoms levels over time. Growth curve modeling was implemented using SAS PROC MIXED with and random slopes and intercepts, and time expressed as a continuous variable (in years from baseline). First, separate base models (adjusted for age and study site) assessed crude associations between latent activity rhythm sub-groups with the level and rate of change in the outcome over time (associations with the rate of change were examined as the interactions between activity rhythm sub-group and time). Associations between all covariates with the level and rate of change in the outcome were similarly assessed. From these separate models, a maximum multivariable was constructed including all associations that achieved at least $p<0.10$ with the level (intercept) or rate of change (slope) in depression symptoms over time.

TABLE 1. Item–response probabilities conditional on latent group membership ($n = 3001$).

	Early acrophase	Early up-mesor	Early down-mesor	Late acrophase	Late up-mesor	Late down-mesor	Low st. amp.	Low mesor	Low amp.	Low psuedo-*F*	High alpha
Group name											
Normal rhythm	0.01	0.26	0.01	0.01	0.04	0.12	0.07	0.11	0.01	0.05	0.01
Low activity	0.10	0.37	0.01	0.01	0.02	0.15	0.38	0.78	0.86	0.62	0.02
Early activity	0.99	0.88	0.48	0.01	0.01	0.01	0.16	0.13	0.05	0.13	0.01
Early/short active period	0.76	0.15	0.99	0.01	0.20	0.01	0.31	0.02	0.01	0.12	0.96
Early/short active period/dampened	0.88	0.35	0.99	0.01	0.17	0.01	0.88	0.44	0.99	0.73	0.82
Late activity	0.01	0.01	0.01	0.99	0.50	0.85	0.08	0.10	0.01	0.08	0.02
Late/short active period	0.01	0.01	0.34	0.32	0.95	0.01	0.29	0.18	0.24	0.28	0.99
Late with low activity	0.01	0.01	0.01	0.99	0.64	0.88	0.50	0.77	0.87	0.73	0.06

Acrophase, time of day of peak activity level; up-mesor, time of day when activity passes up through mesor (approximating the time the participant ''gets going'' in the morning); down-mesor, time of day when activity passes down through mesor (approximating the time of day the participant ''settles down'' for the night); amplitude, peak-nadir difference (rhythm height); mesor, estimated middle of the fitted curve; standardized amplitude, amplitude divided by mesor (lower values indicate a dampened rhythm); pseudo-*F*, robustness of the activity pattern (lower values indicating poorer model fit); alpha, the relative width of the activity peak compared with nadir (higher values indicate a relative narrowness of the active compared with rest period)

To achieve a parsimonious final model, variables which were not significantly associated with the outcome in the maximum model ($p < 0.10$) were removed. The covariates included in the final model are listed at the bottom of Table 3.

RESULTS

Latent class analysis

Activity rhythm variables were best modeled using eight groups (Supplementary Table 1). Groups were assigned names based on examining conditional item–response probabilities (Table 1). For descriptive purpose, activity data with the modeled rhythm are presented (Figure 1) from single subjects representing each of the derived sub-groups.

The largest group had normative activity rhythms (as indicated by low probabilities of being in any extreme quartile) and were labeled the ''normal rhythm'' group (32.09% of the sample; Panel A in Figure 1).

One group had indications of low rhythm height (high probability of low mesor and amplitude with an intermediate probability of low robustness) and was labeled ''low activity'' (10.06%; Panel B in Figure 1); note that this group had lower probabilities of having standardized amplitude and low probabilities of non-normative timing.

Two groups appeared to have non-normative timing but no other indication of abnormal activity rhythms: one group had earlier activity peaks and up-mesor, plus an intermediate probability of an earlier down-mesor (''early activity'', 10.53%; Panel C in Figure 1). Another group had later activity peaks and down-mesors with an intermediate probability of a later up-mesor (''late activity'', 14.46%; Panel F in Figure 1).

Two groups had altered timing and a shorter active period. Of these groups, one had an earlier peak and down-mesor combined with a high alpha (''early/short active period'', 9.63%; Panel D in Figure 1). Another group had a later up-mesor with a short active period (''late/short active period'', 8.23%; Panel G in Figure 1).

The final two groups had later or earlier activity similar to groups described above, except that these last groups also had indication of lower rhythm height (high probabilities of low rhythm height/robustness). One group (''early/short active period/dampened'', 6.80%; Panel E in Figure 1) had high probabilities of having an earlier activity timing, plus a high alpha (indicating a shorter active period) and low rhythm height (both standardized amplitude and robustness). The remaining group had later activity, plus a high probability of low height/robustness (''late with low activity'', 8.20%; Panel H in Figure 1).

To further examine between-group differences indicated by the item–response probabilities, we examined activity rhythm characteristics expressed continuously and stratified by LCA-derived sub-group (see bottom of Table 2). Substantial differences in mean activity rhythm characteristics by group were apparent and consistent with the conditional item–response probabilities. For descriptive purposes, health characteristics that were entered in the final longitudinal model are also shown by activity rhythm sub-group (Table 2).

Growth curve model

The final follow-up assessment was conducted an average of 5.5 years (0.52 SD) after baseline. In the crude model (Table 3), the following sub-groups had faster increases in depressive symptoms over time (this and all subsequent comparisons are with the ''normal rhythm'' group which was set as the reference sub-group): ''low activity'', ''late activity'', ''late/short active period'', ''early/short active period/dampened'' and ''late with low activity''. In other words, before covariate adjustment, compared with the ''normal rhythm'' group, all groups with non-normative parameters

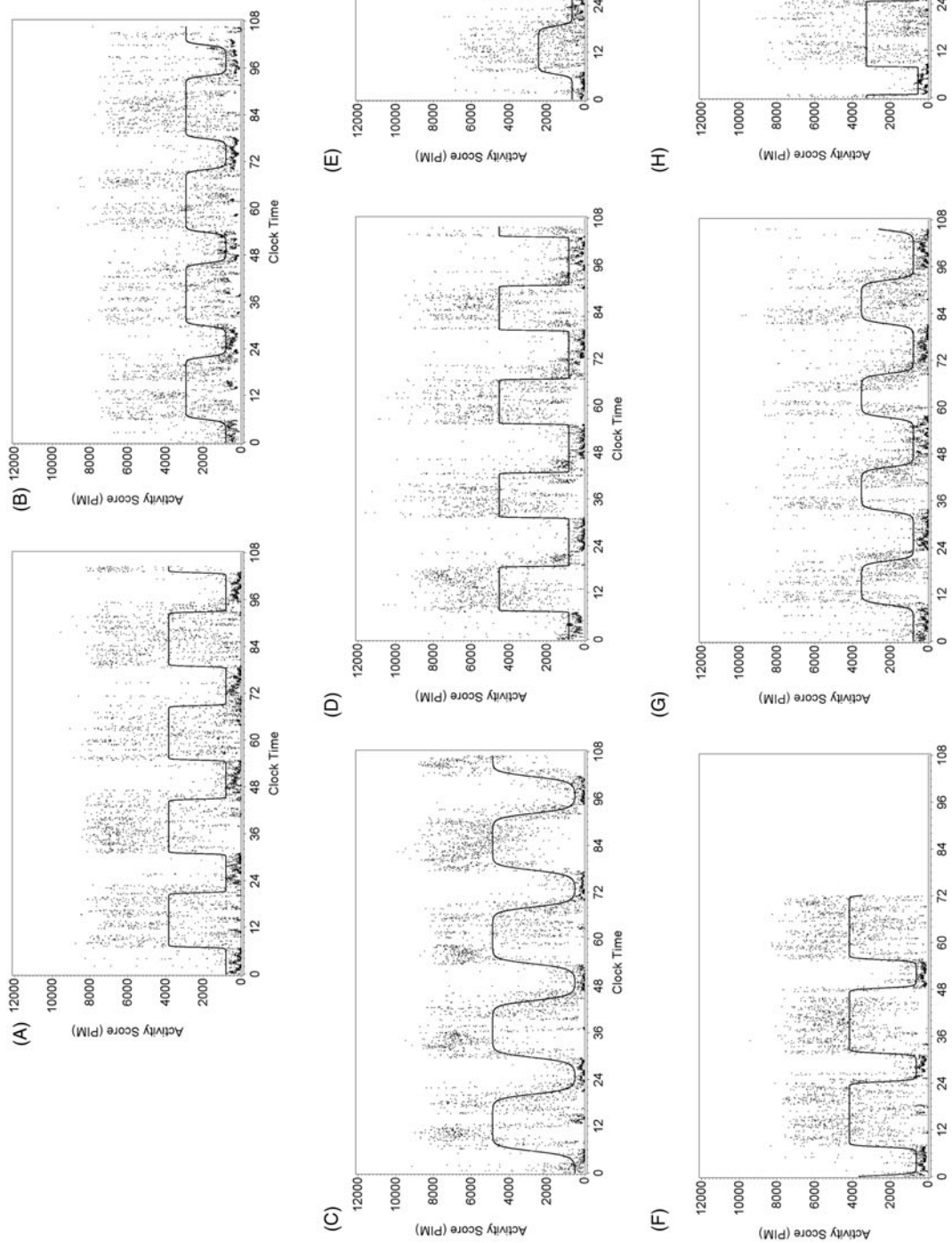

FIGURE 1. Modeled activity rhythms of eight men representing the data-derived sub-groups. Activity data and the modeled rhythm are plotted over time. The eight men belonged to the following groups: Panel A, normal rhythm; Panel B, low activity; Panel C, early activity; Panel D, early/short active period; Panel E, early/short active period/dampened; Panel F, late activity; Panel G, late/short active period; Panel H, late/low activity.

TABLE 2. Descriptive characteristics by activity rhythm sub-groups (total $n = 3001$), mean (SD) shown unless otherwise noted.

	Normal rhythm	Low activity	Early activity	Early/short active period	Early/short active period/ dampened	Late activity	Late/short active period	Late with low activity
	32.09 (963)	10.06 (302)	10.53 (316)	9.63 (289)	6.80 (204)	14.46 (434)	8.23 (247)	8.20 (246)
Age	75.76 (5.26)	78.31 (5.88)	75.32 (5.07)	75.92 (5.14)	77.55 (5.6)	75.71 (5.33)	76.48 (5.39)	78.13 (6.3)
BMI	26.65 (3.51)	27.46 (4.16)	27.02 (3.61)	27.4 (3.41)	28.73 (4.45)	26.93 (3.92)	27.85 (3.99)	27.78 (4.18)
Cognitive function	93.35 (5.42)	91.87 (7.14)	93.1 (5.22)	92.66 (5.55)	91.06 (7.84)	93.56 (5.13)	91.6 (6.55)	92.05 (6.36)
Anxiety symptoms	0.87 (1.78)	1.05 (1.93)	0.85 (1.72)	1.04 (1.88)	0.74 (1.65)	0.88 (1.85)	1.39 (2.28)	1.43 (2.31)
PSQI	5.23 (2.96)	5.97 (3.43)	5.35 (3.35)	5.63 (3.22)	5.98 (3.62)	5.43 (2.96)	6.32 (3.71)	6.46 (3.74)
Physical Activity	159.02 (70.38)	121.61 (69.07)	167.34 (78.8)	154.89 (66.42)	123.76 (65.77)	145.14 (65.59)	143.51 (72.29)	107.73 (62.83)
IADL impairment	0.18 (0.58)	0.54 (0.96)	0.29 (0.73)	0.24 (0.6)	0.56 (1.07)	0.3 (0.76)	0.56 (1.09)	0.86 (1.22)
COPD, *n* (%)	32 (3.32)	27 (8.94)	20 (6.33)	11 (3.81)	13 (6.40)	21 (4.84)	16 (6.48)	17 (6.91)
Fall in past 12 months, *n* (%)	254 (26.38)	103 (34.11)	85 (26.90)	73 (25.26)	62 (30.54)	143 (32.95)	89 (36.03)	95 (38.62)
Diabetes, *n* (%)	112 (11.63)	50 (16.56)	28 (8.86)	38 (13.15)	37 (18.23)	54 (12.44)	38 (15.38)	44 (17.89)
Parkinson's, *n* (%)	7 (0.73)	7 (2.32)	0 (0)	0 (0)	7 (3.45)	2 (0.46)	5 (2.02)	8 (3.25)
Severe SDB, *n* (%)	128 (14.21)	7 (21.91)	35 (11.74)	46 (16.55)	48 (24.37)	68 (16.96)	48 (20.51)	59 (25.99)
Activity rhythm variables								
Acrophase	14.29 (0.39)	14.19 (0.53)	12.97 (0.55)	12.99 (0.65)	12.71 (0.95)	15.66 (0.65)	14.66 (0.72)	15.99 (1.16)
Up-mesor	6.71 (0.61)	6.5 (0.8)	5.54 (0.79)	7.08 (0.83)	6.82 (1.21)	7.88 (0.85)	8.83 (1.15)	8.3 (1.47)
Down-mesor	21.86 (0.68)	21.88 (0.79)	20.4 (0.73)	18.89 (1.16)	18.6 (1.54)	23.44 (0.85)	20.49 (1.12)	23.68 (1.23)
Amp.	3953.75 (658.03)	2529.92 (450.64)	3839.14 (703.04)	4290.21 (1241.03)	2296.71 (466.29)	3868.43 (642.66)	4275.28 (1738.7)	2429.83 (537.53)
Mesor	2234.51 (329.52)	1688.58 (322.48)	2237.79 (368.08)	2606.41 (609.99)	1917.22 (398.34)	2213.97 (304.36)	2511.47 (760.59)	1682.3 (315.54)
St. Amp.	1.78 (0.19)	1.53 (0.29)	1.73 (0.23)	1.65 (0.26)	1.22 (0.25)	1.75 (0.18)	1.68 (0.33)	1.46 (0.30)
Pseudo-*F*	1282.27 (495.09)	628.59 (227.38)	1163.29 (511.24)	1200.96 (501.88)	576.59 (223.78)	1173.9 (411.5)	1003.51 (515.46)	584.5 (216.95)
Alpha	−0.40 (0.12)	−0.42 (0.14)	−0.36 (0.13)	0.07 (0.29)	0.03 (0.25)	−0.44 (0.14)	0.13 (0.34)	−0.41 (0.20)

Note: Selected health characteristic are those that entered the final model predicting depression severity over time;

SD, standard deviation; acrophase, time of day of peak activity level; up-mesor, time of day when activity passes up through mesor (approximating the time the participant ''gets going'' in the morning); down-mesor, time of day when activity passes down through mesor (approximating the time of day the participant ''settles down'' for the night); amplitude, peak-nadir difference (rhythm height); mesor, estimated middle of the fitted curve; standardized amplitude, amplitude divided by mesor (lower values indicate a dampened rhythm); pseudo-*F*, robustness of the activity pattern (lower values indicating poorer model fit); alpha, the relative width of the activity peak compared with nadir (higher values indicate a relative narrowness of the active compared with rest period).

TABLE 3. Crude and adjusted associations of individual predictors with the rate of change in depressive symptoms.

	Crude model[a] ($n = 2933$)		Adjusted Model[b] ($n = 2700$)	
	Predictor * Time		Predictor * Time	
Circadian activity rhythm latent class	β (SE)	*p* value	β (SE)	*p* value
Normal rhythm	Reference		Reference	
Low activity	**0.10 (0.03)**	**0.0004**	0.04 (0.03)	0.21
Early activity	−0.01 (0.03)	0.66	−0.02 (0.03)	0.47
Early/short active period	0.03 (0.03)	0.34	0.01 (0.03)	0.65
Early/short active period/dampened	**0.13 (0.03)**	**<0.0001**	**0.09 (0.03)**	**0.01**
Late activity	**0.05 (0.02)**	**0.02**	**0.05 (0.02)**	**0.03**
Late/short active period	**0.12 (0.03)**	**<0.0001**	**0.06 (0.03)**	**0.03**
Late with low activity	**0.13 (0.03)**	**<0.0001**	**0.07 (0.03)**	**0.02**

[a]Adjusted for: age and study site.
[b]Adjusted for: age, study site, baseline depression severity, BMI, self-reported physical activity, cognitive function, anxiety symptoms, self-reported sleep quality, percent time in rapid eye movement sleep, stressful events (loss of a pet, separated from child who is depended on, serious financial trouble, anything else), social factors (weekly participation in group, number of relatives), chronic diseases (IADL Impairment, COPD, fall in past 12 months, diabetes, Parkinson's, severe SDB), medication use (antidepressant use, benzodiazepine use, non-benzodiazepine non-barbiturate sedatives/hypnotics). Bold indicates $p < 0.05$

except for ''early activity'' and ''early/short active period'' had significantly greater longitudinal increases in average depression symptoms levels when compared with the normative rhythm group.

The final model included all covariate associations with the level or rate of change that retained significance in the maximum model. After covariate adjustment, the association of ''low activity'' with faster depression symptoms increases was attenuated and no longer statistically significant (Table 3). All other associations between activity rhythm sub-groups retained significance levels after adjustment. Expressing actigraph and PSG sleep variables as continuous variables did not alter these results. Being in any group with late activity [''late activity (only)'', ''late/short active period'' and ''late with low activity''] was associated with significantly higher annual increases in overall depressive symptomology (Table 3). Being in the ''early/short active period/dampened'' sub-group also remained significantly associated with faster symptom increases over time. These interactions are illustrated (Figure 2) as adjusted mean predicted depression symptom scores shown by activity rhythm sub-group over time. Mean GDS scores in each group by time point are also included for descriptive purposes (Supplementary Table 2).

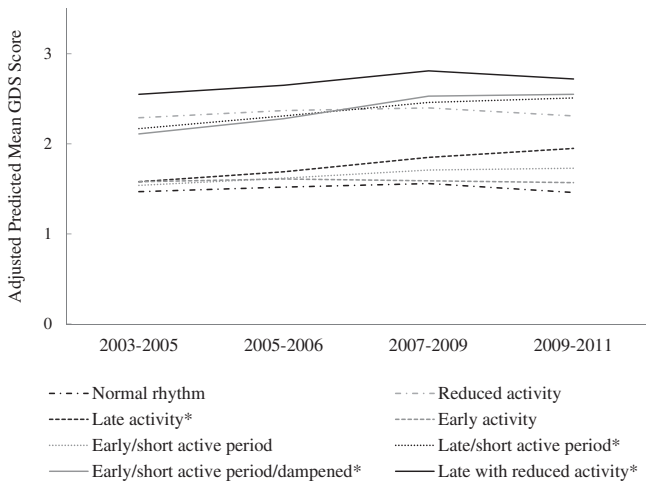

FIGURE 2. Adjusted predicted mean GDS scores by CAR sub-groups over time. Note the scale of the y-axis was modified from that of the GDS (range: 0–15) to visually illustrate the significant interactions wherein four CAR sub-groups (marked with an asterisk) have greater average subject-specific slopes by CAR sub-group compared with the normal rhythm group.

DISCUSSION

We used a person-centered, data-driven clustering approach (LCA) to identify sub-groups of older men who had similar patterns of co-occurring activity rhythm disturbances. This approach produced intuitive and novel insights into the types of activity rhythm disturbances that are common among older men. Although replication in other samples is necessary, we identified eight sub-groups which had distinct activity rhythm characteristics and differing depression risk.

In our sample, timing variables had a role distinguishing activity rhythm sub-groups (i.e. into ''larks'' or ''owls''). Having a narrow active period and/or low rhythm height/robustness appeared to further distinguish the derived sub-groups. Note that rhythm robustness (measured with the pseudo-*F* statistic) and the unstandardized rhythm height measures separated sub-groups in the same pattern. That is, sub-groups with a lack of rhythm robustness appeared to also have less activity overall, and vice versa. Future longitudinal research is needed to determine if low rhythm robustness (regularity) precedes or results from activity reductions.

In this study, we found that having low activity height/robustness alone was associated with an increased burden of depressive symptoms over time,

but that this association was accounted for by covariate adjustments including lifestyle and health factors. Note that this finding is consistent with our previous study which found that an association between low rhythm amplitude and future depression was accounted for by concurrent health status covariates (Smagula et al., 2015).

This work also found that men with indication of more delayed activity rhythms experienced significantly faster increases in depressive symptoms over time, independent of chronic diseases, night-time sleep characteristics and self-reported physical activity; when later activity timing was accompanied by either a compressed active period or low activity levels, depressive symptom increases appeared somewhat faster (compared with having later activity timing alone). Note that having delayed timing was related to future depressive symptoms even in the men with a normative active period length; this suggests that it is not necessarily that staying up later results in an excessive build-up of homeostatic drive, but rather, potentially a mismatch between the sleep–wake cycle and the internal clock/exogenous cues that is depressogenic in these men.

In addition, we found that having earlier timing, only when combined with a dampened rhythm and short active period, was independently associated with an increasing burden of depressive symptoms. This group most clearly underscores the utility of our data-driven approach: early activity timing and rhythm height reductions were only independently associated with faster depressive symptom accumulation when co-occurring (Table 3). Early activity in this group is consistent with the hypothesis that depression is associated with a phase advance in cortisol and norepinephrine secretion (Koenigsberg et al., 2004). Noting that early activity timing itself was not related to depression, advances in circadian physiological arousal may only occur or be associated with depression when accompanied by a dampened activity rhythm amplitude and a shorter active period. These reductions in rhythm height and the duration of the active period may reflect an inability to maintain wakefulness at appropriate times due to a lack of exogenous timing cues (such as daytime light and social interaction), an insensitivity to them, or a loss of endogenous clock control over behavior.

This study has several key advantages over our previous investigation (Smagula et al., 2015), which was limited to a short-term follow-up (an average of 1.2 years), and only examined activity rhythm disturbances separately. In our previous investigation, rhythm robustness (measured with the pseudo-*F* statistics) was the only activity rhythm parameter that independently predicted depressive symptom increases. This work now clarifies that low rhythm robustness is independently associated with faster depressive symptom increases only when accompanied by other alterations, specifically as in the ''Late with low activity'' or ''Early/short active period/dampened'' groups. Our earlier study may have thus detected a sub-group at risk due to low rhythm height/robustness that heterogeneously combined with delayed or advanced activity timing.

Our previous study also failed to detect an association between activity timing delays and future depressive symptoms. Again, the current findings clarify by suggesting depression risk is only elevated when older men have multiple measures of their modeled activity rhythm affected (e.g. having both acrophase and down-mesor later); because our prior study only investigated timing variables (up-mesor, acrophase and down-mesor) separately, this may have adversely affected the available signal and added noise (e.g. by including individuals in each timing parameter's disturbance group when they had normal activity timing on 2/3 measures). Alternatively, it is possible that discrepancies between the current and past findings reflect differences in the nature of activity rhythm-related depression risk over short (1.2 years in our previous study) and longer (>5 years in this study) terms. Although future research is needed to conclusively establish the roles of activity rhythm disturbances in relation to depression risk, our current findings suggest that examining multiple activity rhythm characteristics is more informative than examining individual activity rhythm characteristics alone.

Several limitations should be highlighted, including the current need to confirm the existence, prevalence, and health-relevance of the identified activity rhythm disturbances combinations in independent samples. Actigraph-recorded activity rhythms reflect the activity of the master biological keeper in the suprachiasmic nucleus, but should not be interpreted as a direct indicator of circadian biology (Ancoli-Israel et al., 2003). The MrOS Sleep Study consists of older men who were mostly white, and these findings cannot necessarily generalize to other populations. The derivation of sub-groups via LCA and subsequent use of these sub-groups to predict change in a longitudinal mixed model introduces measurement error. However, any such classification error would potentially reduce the available signal (potency of the true activity rhythm configurations) and bias our results to the null. Residual confounding may have influenced our results, in particular, our analysis did not account for a potential role of past depressive episodes in relation to current activity rhythms and future depression symptoms. The average magnitude of depression severity and changes in severity associated with these activity rhythm groups was not large (Figure 2). However, it is worth noting that the increased rate of symptom change independently associated with four activity rhythm sub-groups (discussed above) was comparable with that of traditional depression risk factors identified in our sample [and included in the final model, i.e. diabetes, past year fall and a lack of participation in social groups]. Our analysis examined differences in the average subject-specific

slope of change in overall depression symptom severity and did not test whether activity rhythm sub-groups were related to distinct patterns of symptom accumulation (i.e. if the sample was composed of mixtures of slope parameter distributions) or the incidence of clinical depression.

Strengths of our study include the large, population-based sample that was comprehensively characterized at baseline and followed up over a substantial time period (of >5 years). Our innovative application of LCA adds substantively to past literature which has focused on each aspect of the activity rhythm separately. This novel data-driven approach demonstrated that among older men, activity rhythm disturbances are highly co-morbid and tend to co-occur in specific and objectively measurable patterns. Our longitudinal analysis revealed that later timing or early/compressed/dampened activity rhythms were independently related to depression risk. Sub-groups with lower rhythm height/robustness, and/or shorter active periods may have resulted from losses in the integrity or effectiveness of the central circadian output to regulate behaviors (Hofman, 2000; Monk & Kupfer, 2000; Münch et al., 2005). However, little is known regarding how activity rhythm disturbances develop and future research is also needed determine how different combinations activity rhythm disturbances might synergistically affect depression and other aspects of health.

Our findings raise important questions regarding how activity rhythms are mechanistically involved in the pathogenesis of depression. We observed that grossly different activity rhythm profiles (e.g. groups with earlier and later timing) were both associated with depression risk. It is possible these differences in the nature of activity rhythm disturbance associated with depression risk may signal heterogeneous etiological pathways which lead to similarly heterogeneous clinical presentations of major depressive disorder. Determining the relevance of activity rhythm disturbances to depression will require resolving how activity rhythms relate to the known biological, psychological and social determinants of health. Research in this spirit is already underway (e.g. Oosterman et al., 2008; Sherman et al., 2015; Zuurbier et al., 2015), and in the future may help establish more precise pathways linking circadian disruption, activity rhythm patterns and depression. Even without knowledge of precisely how activity rhythms relate to depression, because the activity rhythm appears to be a modifiable and independent contributor to the development of depression symptoms, future research targeting the activity rhythm for depression prevention is warranted.

DECLARATION OF INTEREST

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