Sleep and physiological dysregulation: a closer look at sleep intraindividual variability

Running title: Sleep variability and physiological dysregulation

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**ABSTRACT**

**Study Objectives:** Variable daily sleep (i.e., higher intraindividual variability; IIV) is associated with negative health consequences, but potential physiological mechanisms are poorly understood.  This study examined the associations between sleep timing, duration, and quality IIV and physiological dysregulation, with diurnal cortisol trajectories as a proximal outcome, and allostatic load (AL) as a multi-system distal outcome.

**Methods:** Participants are 436 adults ($M_{age}\pm SD$=54.1±11.7, 60.3% women) from the Midlife in the United States study. Sleep was objectively assessed using 7-day actigraphy. Diurnal cortisol was measured via saliva samples (4/day for 4 consecutive days).  AL was measured using 23 biomarkers from 7 systems (inflammatory, HPA, metabolic glucose and lipid, cardiovascular, parasympathetic, sympathetic) using a validated bi-factor model.  Linear and quadratic effects of sleep IIV were estimated using a validated Bayesian model.

**Results:** Controlling for covariates, more variable sleep timing ($p$=.04 for risetime, $p$=.097 for bedtime) and total sleep time (TST; $p$=.02), but not mean sleep variables, were associated with flatter cortisol diurnal slope.  More variable sleep onset latency and wake after sleep onset, later average bedtime, and shorter TST were associated with higher AL adjusting for age and sex ($p$-values<.05); after controlling for all covariates, however, only later mean bedtime remained significantly associated with higher AL ($p$=.04).

**Conclusions:** In a community sample of adults, more variable sleep patterns were associated with blunted diurnal cortisol trajectories, but not with higher multi-system physiological dysregulation. The associations between sleep IIV and overall health are likely complex, including multiple biopsychosocial determinants, and require further investigation.

*Keywords:* intradividual variability, sleep, cortisol, allostatic load, health, physiological dysregulation.

**STATEMENT OF SIGNIFICANCE**

This is the first adult study that examined the associations between (1) sleep variability with diurnal cortisol, and (2) objectively-measured sleep (mean and variability) and allostatic load, an index of multi-system physiological dysregulation. More variable sleep timing and duration were associated with flatter diurnal cortisol trajectories, which are linked with poor health outcomes including mortality. After account for confounders, later average bedtime but not sleep variability was associated with higher AL. Sleep variability is associated with a biomarker strongly influenced by sleep and circadian regulations, but less so with broad, multi-system measures. These findings shed light on potential physiological mechanisms linking sleep and health, and suggest that such relationships are complex, and requires further investigation.

**INTRODUCTION**

Sleep plays a critical role in physical health. Reviews highlight the wide-ranging effects of sleep, such as on the immune system [1,2], incidence of diabetes [3] and cardiovascular diseases [4], and all-cause mortality [5]. There are three main gaps in the literature with regards to sleep and physical health: (1) a strong focus on the effects of mean sleep timing, duration, or quality, and a lack of integration of intraindividual variability (IIV; day-to-day variability) of these sleep domains as an important second dimension; further, as distinctive dimensions, sleep timing, duration, quality and their IIV are often examined in isolation, (2) a lack of understanding of underlying physiological mechanisms, and (3) a strong focus on specific health conditions, and a lack of understanding of sleep in relation to overall physiology. Using rigorous methodology, this study aims to address these gaps.

**Sleep IIV and Physical Health: What Do We Know**

Sleep/wake patterns are influenced by biological processes that are relatively stable (e.g., the homeostatic sleep drive rises with increasing time awake, the circadian process typically synchronized to the dark–light cycles [6]), as well as a wide range of factors (e.g., work schedules, psychopathology, personality traits, physical illness) that contribute to their day-to-day variations (see Bei et al., 2016 [7] for a systematic review). There is growing recognition that the IIV of sleep, as a second dimension alongside the intraindividual means (IIM; average values across days; e.g., sleep duration mean), might be relevant to physical health. Throughout this paper, IIV is referred to as a continuous (rather than categorical) dimension, with greater/higher IIV indicating more day-to-day variability.

Variable sleep patterns are commonly associated with chronic sleep restriction and circadian misalignment (i.e., sleep occurring outside of optimal circadian phase), both of which are consistently linked to negative health outcomes [8,9]. The handful of studies that directly examined the associations between sleep IIV and physical health showed that in community-dwelling older adults, more variable sleep timing and duration were associated with higher rates of diabetes, heart conditions, higher body mass index and rates of obesity, poorer self-reported health [10], as well as higher pro-inflammatory biomarkers interleukin-6 (IL-6) and tumor necrosis factor alpha (TNF-α) [11]. The relevance of sleep timing/duration IIV to glucose regulation is evident in several populations: more variable total sleep time (TST) was associated with higher glycated hemoglobin in older adults with short-sleep insomnia [12], more variable bedtime (BT) was associated with higher homeostatic model assessment-insulin resistance (HOMA-IR) in middle-aged women [13], and more variable sleep duration/timing were associated with poorer glycaemic control in patients with Type 1 Diabetes [14]. Therefore, there is evidence that more variable sleep is related to specific domains of physical health.

**Potential Mechanisms Linking Sleep IIV and Health**

Biomarkers from numerous physiological systems are influenced by sleep and circadian regulation, including epinephrine and norepinephrine of the sympathetic nervous system (SNS) [15,16], heart rate (HR) and HR variability of the parasympathetic nervous system (PSNS) [17], cortisol and dehydroepiandrosterone (DHEA) of the hypothalamic–pituitary–adrenal (HPA) axis [18], IL-6 of the

inflammatory system [19], blood pressure [20], glucose regulation and insulin secretion [21], high and low density lipoprotein cholesterol, as well as triglycerides [22]. These physiological processes are vulnerable to sleep restriction/deprivation and circadian misalignment commonly seen in variable sleep/wake patterns. A carefully controlled experimental study showed that sleep deprivation was associated with higher morning cortisol levels, whereas circadian misalignment was associated with lower morning cortisol levels and higher TNF-α, IL-10, and C-reactive protein (CRP) [23]. Therefore, one potential mechanism linking variable sleep and health is dysregulation of physiological processes through sleep and circadian disruptions.

A second potential mechanism is repeated activation of allostatic process. Many physiological systems are tightly regulated as they operate effectively within only a narrow window (homeostasis; e.g., a 4-degrees change in core body temperature has a profound impact). Allostasis describes the process of physiological systems maintaining stability under changing demands [24] and is critical for maintaining homeostasis. Although allostasis is adaptive, it is theorized that frequent and repeated activation of allostatic processes results in wear-and-tear on the system, termed allostatic load (AL) [25]. Highly variable sleep/wake patterns require the system to adapt to changing demands, which if occurs frequently, could theoretically cause wear-and-tear on the system. The AL model further posits that repeated and prolonged activation of allostasis ultimately results in dysregulation across multiple physiological systems (e.g., cardiovascular, immune, lipid, metabolic, glucose metabolic, etc.), with the HPA axis and cortisol (a glucocorticoid) and catecholamines serving as primary mediators of this process [26].

Therefore, in this study, two outcomes are considered for sleep IIV: cortisol as a proximal outcome, and AL as a distal outcome.

### Cortisol

Both the aforementioned sleep/circadian and allostatic processes point to dysregulation in the HPA axis, which can be measured via cortisol levels. There is evidence that mean sleep duration may be associated with the cortisol awakening response (CAR) [27,28] and its decline across the waking day [27,29,30], but how diurnal cortisol trajectories are associated with sleep IIV is rarely examined. To the best of our knowledge, there is only one study to date that examined the association between sleep IIV with diurnal rhythms of biomarkers. In 76 older adolescents, more variable sleep duration assessed over 4 days using actigraphy was associated with lower levels of waking cortisol and flatter diurnal slopes across the day [31]. How other aspects of sleep IIV (e.g., timing, quality) are associated with cortisol diurnal trajectories, and what these associations may be like in adults remain unknown.

### Allostatic Load

Dysregulation in diurnal cortisol may lead to pervasive multisystem physiological dysregulation, as cortisol is a potent regulator of multiple physiological processes (e.g., the immune system [32]). Multi-system physiological dysregulation (AL) can be indexed using a composite index of biomarkers across multiple physiological systems [33]. There is robust evidence of substantial shared variance across

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biomarkers of multiple systems [34–36], further validating the utility of a multi-system measure that captures AL.

Sleep and circadian disruption have been conceptualized as key drivers of AL [37]. This is supported by empirical evidence that in community-dwelling adults, the presence of sleep disturbances (e.g., sleep apnea, insomnia) was associated with significantly higher AL [38,39], and that AL improved after cognitive behavioural therapy for insomnia [40]. These existing studies focused on the mean levels of sleep disturbances and duration, and the association between sleep IIV and higher AL (i.e., greater multi-system physiological dysregulation) has not yet been examined.

**Current Study**

Using a sample of community dwelling adults, the current study aims to assess the associations between objectively measured sleep IIV and (a) cortisol diurnal rhythm as a proximal outcome, and (b) a multi-system physiological dysregulation index (i.e., AL) as a distal outcome. It was hypothesized that accounting for relevant covariates, more variable BT, risetime (RT), TST, sleep onset latency (SOL), and wake after sleep onset (WASO) would be associated with (a) flatter diurnal cortisol trajectory and (b) higher AL. To examine unique effects of sleep IIV above the means, the IIM of respective sleep variables were controlled for and their effects simultaneously examined. Finally, both linear and quadratic effects of the mean and IIV of sleep variables were tested, because: (a) Average sleep levels (especially TST [41]) may share a non-linear relationship with health; (b) Whilst our primary hypotheses link more variable sleep to worse health outcomes, some researchers suggest that greater IIV may be adaptive in some contexts [42,43]. For example, Hartmann (1973)[43] reported that in some individuals, sleep requirements may increase during periods of high stress and decrease during low stress, and such variation may be adaptive given the restorative function of sleep.

**METHODS**

Samples in this study were drawn from the Midlife in the United States Study 2 (MIDUS 2), a 10-year follow-up of MIDUS 1, which collected data from a nationally representative random-digit-dial sample of non-institutionalized, English-speaking adults; MIDUS 2 also included an over-sample of African Americans from Milwaukee, Wisconsin, stratified according to the proportion of African Americans.

Participants from MIDUS 2 were eligible for the biomarker substudy, which was conducted across three sites. Only the University of Wisconsin-Madison site collected actigraphy data in addition to measures of AL, hence all participants in this study come from the catchment area for this site. A subset of participants also completed the second wave of the National Study of Daily Experiences substudy, for which all participants from MIDUS 2 were eligible; these participants contributed to the cortisol analyses in this study.

Details on MIDUS [44,45], as well as procedures in the collection of cortisol [46] and AL-related biomarkers [45] can be found in previous publications.

**Equipment and Materials**

*Sleep*

Sleep was assessed using actigraphy, a well-validated objective method that estimates sleep duration and quality via wrist-movements [47,48]. Participants were asked to start actigraphy measurement from 7:00 AM on the Tuesday after returning home following their visits to the clinical/translational research center units where blood, urine, and other biomarkers were collected (i.e., there is a minimum one night between the visit and the start of actigraphy recording). They were asked to wear the actigraph on the non-dominant wrist for 7 consecutive days and nights, register BT and RT using the event marker and complete sleep diary everyday, and return the watch in a prepaid envelope.

Specifically, the Mini Mitter Actiwatch®-64 were used to collect data on the non-dominant hand using 30-sec epochs for 7 days continuously. Concurrent sleep diary and Event Markers on the Actiwatch were used to manually determine BT and RT. Actiware 5 was used to generate the following variables based on medium threshold for sleep/wake detection: BT, RT, TST, SOL, WASO, and sleep efficiency (SE)[1].

The IIM and IIV of sleep variables was modelled using a purpose built and validated Bayesian framework [49,50], using all available data and accounting for measurement error. A summary of the IIV analysis is in the *Supplemental Material*.

*Cortisol*

Diurnal cortisol was assessed on 4 out of 8 days as part of the National Study of Daily Experiences 2 substudy of MIDUS. Specifically cortisol was assessed based on saliva samples via the salivette collection devices (Sarstedt, Nümbrecht, Germany) taken at 4 time points across the day: immediately upon awakening (T1), 30 minutes after awakening (T2), before lunch (T3), and at bedtime (T4). Saliva sampling was repeated across 4 consecutive days. Further details on the saliva sampling protocol have been described in previous reports [51,52]. Data were excluded (6.4% of days) if reported time of awakening was missing, or if it was 15 minutes or more after the timing of awakening cortisol.

*Allostatic Load*

Biomarkers for AL were collected during an overnight visit to clinical/translational research center units, during which blood samples, overnight urine samples, anthropometric measures, resting blood pressure, pulse rate, and HR variability were measured as previously described [44,45]. Allostatic load is operationalised as multi-system physiological dysregulation based on 23 biomarkers from 7 systems assessed in the MIDUS 2 Biomarker Project [35]: (1) blood pressure (resting pulse pressure [systolic – diastolic] and systolic blood pressure), (2) glucose (HOMA-IR, fasting glucose, glycosylated hemoglobin),

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[1] Descriptive statistics of SE is shown in the main text, and findings from analyses are included in the Supplemental Materials given its overlap with SOL and WASO.

(3) HPA axis (cortisol and blood serum DHEA-sulfate), (4) inflammation (plasma CRP, IL-6, fibrinogen, soluble E-Selectin, and soluble intracellular adhesion molecule 1), (5) lipids (triglycerides, high- and low-density lipoprotein cholesterol, waist-to-hip ratio), (6) parasympathetic nervous system (resting pulse rate and measures of HR variability, including standard deviation [*SD*] of beat-to-beat intervals, root mean square of successive differences, low- and high-frequency spectral power), and (7) sympathetic nervous system (12-hour overnight urinary epinephrine, norepinephrine).

A previous publication provides further details on each biomarker and a validated bi-factor model [35] which was used for modeling AL as well as 7 system-specific indices, controlling for age and sex. A summary of this model is in the *Supplemental Material*.

### *Covariates*

A number of covariates were considered based on factors related to sleep IIV (see a systematic review [7]) and common covariates assessed in relation to cortisol and AL.  Candidate covariates for cortisol analyses included: sex (women/men), age, race (white/non-white), education, employment status (working/not working), bed partner (yes/no), presence of depression or generalised anxiety disorder (yes/no), current alcohol use (problematic/moderate/none), smoking history (current/past/never), smoking on the day of cortisol measures, physical activity, perceived stress, chronic major medical conditions (count), cortisol medications, waist-to-hip ratio. The above candidate covariates were also tested for AL analyses, except daily smoking and cortisol specific medication were not included; AL relevant medications were included. Age, sex, and waist-to-hip ratio were not included because AL and system specific factor scores have already adjusted/included them [35]. Details on the measurements of covariates are in the *Supplemental Material*.

### Data Analysis

### *Baseline Models*

A piecewise mixed effects model was used, with one slope to capture the CAR (T1 to T2) and a second to capture the Diurnal Slope (T2 to T4).  The model included 4 random effects that were allowed to freely correlate: the intercept (i.e., cortisol at awakening), CAR, Diurnal Slope, and assessment day (cortisol sampling was repeated for 4 days). Residuals were assessed and were approximately normally distributed, therefore untransformed cortisol values were used.

Allostatic load and the 7 system-specific factors based on resting biomarkers were analyzed using linear regression with clustered standard errors to account for some twins and siblings included in the MIDUS sample.  Residuals for AL and the system-specific factors were assessed and were also approximately normally distributed.

### *Unadjusted Models*

Each sleep parameter (BT, RT, TST, SOL, WASO) was tested separately by allowing its IIM and IIV to predict the outcomes in the above baseline models (i.e., cortisol awakening, CAR, and Diurnal Slope for

cortisol analyses; AL and system specific factor scores for AL analyses).  Quadratic relationships were tested by entering the squared individual means and IIVs, and were dropped if not statistically significant.

### Covariates and Adjusted Models

The aforementioned candidate covariates were individually tested to assess whether each of them predicted the outcomes in the baseline models.  Only candidate covariates that were statistically significantly related to the outcomes bivariately were included in the adjusted models.

Data were analysed using R [53] and Mplus v7.3 [54]. See the *Supplemental Material* for specific R packages used. All statistical significance, including that used in analyses for selecting covariates, was determined based on two-tailed *p*-value at .05 with accompanying 95% confidence interval to assist interpretation of uncertainty.

### RESULTS

Actigraphy data were available from a total of 436 adults (age $M \pm SD$ = 54.11 ± 11.67, 60.3% women), with 97.8% daily actigraphy data available.  Compared to the overall sample who provided cortisol or AL data, this actigraphy subgroup had higher percentage of non-white race/ethnicity, but did not differ significantly on age, sex, and cortisol/AL (see detailed comparisons in the *Supplementary Material*).  In this sample, the majority of the sample (70.1%) were Caucasian, 39.0% had college or above education, and over half (56.3%) reported having a bed partner.  They were relatively healthy, most reporting having no (36.7%) or only 1 (28.2%) or 2 (20.9%) major chronic health conditions, and 85.3% were not currently smoking. Descriptive statistics of all variables included in the final models for the overall sample are shown in Table 1 (cortisol, demographics, and covariates) and Table 2 (sleep variables). Distributions of sleep IIV (quantified in model estimated *SD*) are shown in Figure 1. This figure helps practical interpretation of what IIV of sleep "looks like" in the studied sample. For example, for BT, most of the sample had a *SD* of 0.25 − 1.50 hrs.

[TABLE 1, TABLE 2, FIGURE 1 HERE]

### Cortisol

A total of 245 (3261 cortisol samples) participants had measures on cortisol and actigraphy, and among these, 237 (3156 cortisol samples) did not have missing data on any covariates and contributed to both unadjusted and adjusted models.  Quadratic effects of sleep IIM and IIV were not significant for cortisol, so only linear effects were included.  Final covariates included in adjusted cortisol models were: sex, age, race, education, presence of bed partner, smoking history, perceived stress, and the number of chronic major medical conditions.  We also tested an IIV by any chronic major medical condition interaction to examine whether results differed in those with and without a chronic major medical condition.  None of

the interactions were significant and these were dropped in the final analyses. Key findings on cortisol analyses are summarised in Table 3, and full model results (including results on covariates) can be found in Table S1 and S2 in the *Supplemental Material 2 (Tables)*.


[TABLE 3 HERE]


In the unadjusted models, more variable RT, TST, and WASO were all associated with lower cortisol at awakening (all *p*-values < .05), over and above the effects of their respective IIM. None of the sleep IIM or IIV were significantly associated with CAR. On the other hand, more variable BT, RT, TST (all *p*-values < .01), as well as more variable SOL and WASO (both *p*-values < .05) were all independently associated with more positive Diurnal Slope (i.e., flatter trajectory). Additionally, shorter mean TST were also associated with flatter Diurnal Slope (both *p*-values < .05).

The associations found in the unadjusted models were attenuated after controlling for covariates. In the adjusted models, more variable RT (*p* = .040) and TST (*p* = .019) remained significantly associated with flatter Diurnal Slope. Figure 2 illustrate cortisol trajectories for individuals with high and low TST IIV based on the adjusted model.


[FIGURE 2 HERE]


Although no longer statistically significant, there was a trend for more variable RT to be associated with lower awakening cortisol (*p* = .079), and more variable BT (*p* = .097) to be associated with flatter Diurnal Slope. No IIM of sleep variables uniquely predicted cortisol trajectory. Overall, in both the unadjusted and adjusted models, the IIV of sleep variables shared stronger associations with cortisol trajectories than their IIM counterparts.

**Allostatic Load**

A total of 436 participants had measures on AL biomarkers and actigraphy, and among these, 433 did not have missing data on any covariates and contributed to both unadjusted and adjusted models. Quadratic effects of sleep IIM and IIV were not significant for AL, so only linear effects were included. Age and sex were adjusted in the factor scores of AL in all models. In the adjusted model, the following additional covariates were controlled for: race, smoking history, perceived stress, the number chronic major medical conditions, and AL relevant medications. We also tested an IIV by any chronic major medical condition interaction to examine whether results differed in those without and with a chronic major medical condition. None of the interactions were significant and these were dropped in the final

analyses.  Key findings on AL analyses are summarised in Table 4, and full model results (including results on system specific outcomes not already accounted for by AL and findings on covariates) can be found in Table S3 and S4 in the *Supplemental Material*.


[TABLE 4 HERE]


In the models adjusting for only age and sex (i.e., unadjusted models), later mean BT and shorter mean TST were associated with significantly higher AL (all *p*-values < .05).  There were trends for later mean RT, longer mean SOL, and higher mean WASO to be associated with higher AL, but these associations were not statistically significantly (all *p*-values < .1).  Beyond the effects of IIM, more variable SOL and WASO were associated with significantly higher AL (both *p*-values < .05), explaining 2.0%, and 1.6% of additional variance in AL, over and above that accounted for by their respective IIM.  There was a trend for more variable BT to be associated with higher AL (*p* = .076), explaining 1.3% variance in AL independent of its IIM.

Adjusting for additional covariates (i.e., adjusted models), later mean BT (*p* < .05), as well as a trend in later mean RT (*p* < .1) remained associated with higher AL.  However, none of the sleep IIV variables were uniquely associated with AL in the adjusted models.

**DISCUSSION**

This study investigated the associations between sleep IIV and cortisol diurnal rhythm, as well as an index of multi-system physiological dysregulation (i.e., AL). Findings showed that after controlling for covariates, more variable sleep timing and duration was associated with flatter cortisol diurnal slope, over and above the effects of their respective mean values.  More variable sleep quality was associated with higher multi-system physiological dysregulation; however, these associations were no longer significant after controlling for covariates.  Later mean BT was the only sleep IIM significantly associated with higher AL in both unadjusted and adjusted models.  Therefore, in a sample of community-dwelling adults, there is evidence for higher sleep IIV to be associated with alterations in cortisol diurnal rhythm as a proximal outcome, but not with higher multi-system physiological dysregulation as a distal outcome.

**Cortisol**

Findings on cortisol trajectory are consistent with the only other study on sleep IIV and cortisol, showing that in adolescents more variable sleep duration was associated with flatter diurnal slopes and lower levels of waking cortisol [31].  In addition to sleep duration, this study demonstrated that sleep timing IIV may also be relevant to diurnal cortisol trajectory.  Emerging evidence showed that flatter diurnal cortisol trajectories predicted mortality in breast [55] and lung [56] cancer.  In this study, after adjusting for

covariates, a one *SD* change in TST IIV was associated with a .20 *SD* change in diurnal cortisol slope (i.e., a .73 flatter slope, with the overall *SD* of diurnal cortisol slopes being 3.74). To put a .20 *SD* in diurnal cortisol slope into perspective, a large study of public employees found that a one *SD* flatter diurnal cortisol slope predicted mortality with a hazard ratio of 1.30 [57].

After controlling for covariates, IIV in sleep quality-related domains (i.e., SOL and WASO) was not significantly associated with cortisol trajectories. It is possible that cortisol, a biomarker with strong circadian influence, is more sensitive to disturbance to sleep duration and timing, compared to disturbance to sleep at the start (i.e., SOL) or middle (i.e., WASO) of the primary sleep period. It is also possible that the association between sleep quality IIV and cortisol outcomes may be evident when sleep is more disturbed/variable than experienced by this relatively healthy community sample.

In both the unadjusted and adjusted models, the IIV of sleep variables shared much stronger associations with cortisol trajectories than their IIM counterparts; in the adjusted model, none of the sleep IIM variables made statistically significant contribution to cortisol trajectories. Previous studies have linked more variable sleep patterns to more evening chronotype [58,59], which is associated with later circadian phase, a risk factor for circadian misalignment [60,61]. It is possible that sleep IIV is specifically associated with circadian misalignment, more so than the IIM of sleep. This may have contributed to the stronger associations between sleep IIV compared to IIM and diurnal cortisol trajectory, which is highly influenced by circadian processes.

**Allostatic Load**

Based on models adjusted only for sex and age, more variable sleep was associated with higher AL as hypothesized. Considered together with the findings that more variable sleep patterns are associated with a blunted cortisol rhythm, the findings are consistent with AL theory positing cortisol dysregulation as a primary mediator between repeated adaptation (i.e., adapting to changing sleep patterns) and dysregulation across multiple physiological systems [26]. These findings are also in line with the body of literature that linked poorer average sleep to higher AL [38], and more variable sleep to specific health outcomes [10–14].

As a distal outcome that is closely associated with overall health, AL is associated with many psychosocial factors in addition to sleep [62]. In the fully adjusted model, most of the significant associations were diminished, suggesting that the association between sleep IIV and multi-system physiological dysregulation is complex, and perhaps driven by one or more common causes. Indeed, several of the covariates included in the fully adjusted model (e.g., race, stress, chronic health conditions) have previously been shown to be related to sleep IIV [49]. For example, in this study, being non-white was associated with significantly higher AL (see Table S4) [2], and previous studies have shown

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[2] Post hoc analysis showed that *race* did not moderate the association between sleep IIV and AL, that is, there was a main effect of *race* on AL, and the association between sleep IIV and AL did not differ significantly between white vs non-white.

non-white or minority race/ethnicity to be associated with more variable sleep [10,63,64], higher AL [65] and worse health [66]. Higher stress was also associated with higher AL in this study, and stress has been previously linked with more variable sleep [64]. It is worth noting that later mean sleep timing was associated with higher AL, even after adjusting for all covariates.

Finally, although chronic conditions were included as a covariate when testing the relations between sleep IIV and AL, it may also be considered as an outcome of AL. Thus, the cross-sectional nature of the data requires caution in interpretation, as whether the additional covariates included in the fully adjusted model are common causes of sleep IIV and AL, or perhaps mechanisms or outcomes of sleep IIV and/or AL is unclear. Our findings that adjusting for age and sex, more variable sleep patterns were associated with higher AL provide evidence for an association, but its nature and causal directions require further research.

**Limitations and Strengths**

Findings in this study need to be interpreted in light of a number of limitations. First, although 7-day actigraphy covers sleep patterns across one week with both weekdays and weekend, it might not be representative of individuals' sleep/wake patterns over longer periods of time. Second, circadian phase was not assessed, and therefore it was not possible to examine the role of circadian misalignment specifically. Third, the cross-sectional nature of the data preclude causal inference. It is also possible that a common cause (e.g., stress) was underlying both variable sleep and elevated biomarkers. Fourth, findings on race may not be generalisable as African Americans in this sample in this study came almost exclusively from Milwaukee (n = 115) with only seven African Americans recruited outside of Milwaukee. Our post-hoc analyses showed that in the larger MIDUS cohort, there were no significant differences between African Americans recruited from Milwaukee (*n* = 188) and those from other sites (*n* = 32) on AL. For cortisol, African American's recruited from Milwaukee (*n* = 116) compared to those from other sites (*n* = 36) had lower initial cortisol levels, but no differences in the CAR or diurnal cortisol slope. Finally, we recognise that not all findings would remain statistically significant using traditional methods of adjustment for multiple comparisons. To assist interpretation of uncertainties, we presented confidence intervals in all findings.

Despite these limitations, the study also had notable strengths. The unique combination of data collected in MIDUS allowed the linkage of objectively measure sleep IIM and IIV, diurnal rhythms of salivary cortisol, and multi-system physiological dysregulation measured by an expansive panel of biomarkers all in a large sample of adults. To our knowledge, this is the first study that examined the associations between sleep IIV with diurnal cortisol rhythms in adults, and the first study to assess the association between objectively measured sleep (both IIM and IIV) and multi-system physiological dysregulation. Rigorous methodologies are the core strengths of this study, these included (a) carefully and comprehensively measured physiological outcomes, (b) quantifying IIV using methods that are robust to missing data and measurement error, (c) accounting for important covariates, which included both the IIM of sleep variables, as well as a set of systematically selected covariates based on prior

evidence, (d) taking into account multiple dimensions of sleep (timing, duration, quality), and (e) the consideration of quadratic effects for both the IIM and IIV of sleep on the outcomes.

In conclusion, in a sample of community adults, more variable sleep timing and duration were associated with flatter diurnal cortisol trajectory, but the association between sleep IIV and multi-system physiological dysregulation appeared weak after accounting for covariates.  The associations between sleep IIV and physiological dysregulation warrant further investigation.  In addition to conducting new studies with a priori hypotheses, future studies could also examine existing datasets, and incorporate IIV as a second dimension to the mean values when daily sleep is examined.

**LIST OF ABBREVIATIONS**

AL = allostatic load

BT = bedtime

CAR = cortisol awakening response

CRP = C-reactive protein

DHEA = dehydroepiandrosterone

HPA = hypothalamic–pituitary–adrenal

HR = heart rate

HOMA-IR = homeostatic model assessment-insulin resistance

IL-6 = interleukin-6

IIM = intraindividual mean

IIV = intraindividual variability

*M* = Mean

MIDUS = Midlife in the United States Study

RT = risetime

*SD* = standard deviation

SE = sleep efficiency

SNS = sympathetic nervous system

SOL = sleep onset latency

TNF-α = tumor necrosis factor alpha

TST = total sleep time

WASO = wake after sleep onset

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**DISCLOSURE STATEMENT**

None.

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**FIGURE CAPTIONS**

*Figure 1*. Sample distributions of intraindividual variability (IIV) for bedtime (BT), risetime (RT), time-in-bed (TIB), sleep onset latency (SOL), wake after sleep onset (WASO), and sleep efficiency (SE).  The sum of areas under the curve is 1 (100%); x-axis shows IIV (i.e., model estimated individual standard deviation).  Shaded regions indicate 95% credible intervals around the estimate.

*Figure 2*. Cortisol trajectories for individuals with high (+1 *SD*) and low (-1 *SD*) total sleep time (TST) intraindividual variability (IIV) based on the adjusted model. Covariates adjusted for are: sex, age, race, education, presence of bed partner, smoking history, perceived stress, and the number of chronic major medical conditions. CAR = cortisol awakening response. Please note that all sleep IIV variables were treated as a continuous (rather than categorical) variable in analyses; this figure displays +/- 1 *SD* in TST IIV to illustrate the difference in trajectories between high/low IIV.

Table 1

*Descriptive Statistics of Cortisol and Included Covariates*

| Variables | Descriptive statistics |
|---|---|
| Sex, *n* (%) [a, b] | Women: 263 (60.3%); Men: 173 (39.7%) |
| Age, *M* (*SD*) [a, b] | 54.11 (11.67) |
| Race, *n* (%) [a, b] | White: 305 (70.1%) |
| | Africa American: 122 (28.0%) |
| | Other: 8 (1.8%) |
| Education, *n* (%) [a] | High school or less: 138 (31.9%) |
| | Some college: 126 (29.1%) |
| | College degree or above: 169 (39.0%) |
| Presence of bed partner, *n* (%) [a] | Yes: 241 (56.3%); No: 187 (43.7%) |
| Smoking history, *n*, (%) [a, b] | Current: 64 (14.7%) |
| | Past: 143 (32.8%) |
| | Never: 229 (52.5%) |
| Perceived stress, *M* (*SD*) [a, b] | 22.68 (6.43) |
| Number of chronic major medical conditions, Median (interquartile range) [a, b] | 1.00 (2.00) |
| Medication relevant to allostatic load, *n* (%) [b] | Yes: 171 (39.2%); No: 265 (60.8%) |
| Cortisol (mmol/L), *M* (*SD*) | Awakening: 12.83 (6.40) |
| | 30 minutes after awakening: 18.31 (8.64) |
| | Before lunch: 7.10 (4.31) |
| | Bedtime: 3.70 (4.20) |

*Note*. Descriptive statics are based on individuals who contributed sleep actigraphy data. a. included in cortisol adjusted models, b. included in allostatic load adjusted models. Selection of covariates was based on preliminary analyses described in text.

Table 2

*Model Estimated Mean (Standard Deviation) for the Intraindividual Mean and Intraindividual Variability of Actigraphy Sleep Variables*

|  | Intraindividual mean | Intraindividual variability |
|---|---|---|
| Bedtime (hour) | 23:26 (1.31) | 1.10 (0.79) |
| Risetime (hour) | 06:28 (1.34) | 1.12 (0.75) |
| Total sleep time (hour) | 6.41 (0.97) | 1.00 (0.42) |
| Sleep onset latency (minute) | 18.78 (11.01) | 31.14 (31.50) |
| Wake after sleep onset (minute) | 43.21 (17.00) | 22.83 (17.75) |
| Sleep efficiency (%) | 80.68 (8.86) | 7.43 (4.47) |

Table 3

*Results of the IIM and IIV of Actigraphy Sleep Variables Predicting Cortisol Trajectory*

| N = 237 | | Unadjusted model | | Adjusted model | |
|---|---|---|---|---|---|
| | | IIM | IIV | IIM | IIV |
| BT | Awakening Cortisol | -0.19, .69 | **-0.94†, .07** | -0.16, .73 | -0.39, .46 |
| | | [-1.11, 0.74] | **[-1.94, 0.06]** | [-1.05, 0.73] | [-1.40, 0.63] |
| | CAR | -0.14, .77 | -0.63, .21 | -0.06, .90 | -0.51, .34 |
| | | [-1.05, 0.77] | [-1.62, 0.36] | [-1.00, 0.88] | [-1.57, 0.54] |
| | Diurnal Slope | 0.18, 58 | **1.01**, .01** | 0.16, .61 | **0.6†, .097** |
| | | [-0.46, 0.82] | **[0.31, 1.72]** | [-0.45, 0.77] | **[-0.11, 1.31]** |
| RT | Awakening Cortisol | 0.04, .93 | **-1.11*, .02** | 0.08, 85 | **-0.84†, .08** |
| | | [-0.85, 0.93] | **[-2.07, -0.16]** | [-0.79, 0.95] | **[-1.78, 0.10]** |
| | CAR | -0.18, .70 | -0.19, .70 | -0.25, .60 | 0.00, .999 |
| | | [-1.07, 0.71] | [-1.15, 0.77] | [-1.17, 0.67] | [-1.02, 1.02] |
| | Diurnal Slope | -0.03, .92 | **0.94**, .01** | 0.03, .92 | **0.67*, .04** |
| | | [-0.65, 0.59] | **[0.28, 1.60]** | [-0.57, 0.63] | **[0.03, 1.31]** |
| TST | Awakening Cortisol | 0.58, .19 | **-1.09*, .02** | 0.40, .37 | -0.73, .12 |
| | | [-0.30, 1.46] | **[-2.01, -0.16]** | [-0.47, 1.27] | [-1.64, 0.19] |
| | CAR | 0.35, .42 | -0.52, .28 | 0.13, .78 | -0.45, .37 |
| | | [-0.50, 1.20] | [-1.47, 0.43] | [-0.77, 1.02] | [-1.44, 0.53] |
| | Diurnal Slope | **-0.71*, .02** | **0.99**, .002** | -0.45, .14 | **0.73*, .02** |
| | | **[-1.31, -0.12]** | **[0.36, 1.62]** | [-1.04, 0.15] | **[0.12, 1.35]** |
| SOL | Awakening Cortisol | -0.28, .62 | -0.39, .45 | -0.16, .76 | 0.17, .74 |
| | | [-1.39, 0.83] | [-1.39, 0.61] | [-1.22, 0.9] | [-0.84, 1.18] |
| | CAR | 0.13, .81 | -0.57, .25 | 0.20, .72 | -0.54, .31 |
| | | [-0.93, 1.19] | [-1.54, 0.40] | [-0.89, 1.29] | [-1.60, 0.51] |
| | Diurnal Slope | 0.04, .91 | **0.76*, .03** | -0.10, .78 | 0.16, .65 |
| | | [-0.69, 0.77] | **[0.08, 1.45]** | [-0.84, 0.63] | [-0.54, 0.86] |
| WASO | Awakening Cortisol | 0.31, .59 | **-1.25*, .04** | 0.28, .61 | -0.65, .26 |
| | | [-0.83, 1.46] | **[-2.41, -0.09]** | [-0.80, 1.36] | [-1.80, 0.49] |
| | CAR | -0.64, .23 | -0.19, .73 | -0.65, .24 | -0.02, .98 |
| | | [-1.67, 0.39] | [-1.28, 0.89] | [-1.73, 0.43] | [-1.18, 1.15] |
| | Diurnal Slope | 0.45, .23 | **0.84*, .03** | 0.34, .37 | 0.32, .41 |
| | | [-0.29, 1.18] | **[0.11, 1.57]** | [-0.39, 1.07] | [-0.44, 1.07] |

*Note.* Unstandardized coefficients, *p*-values [95% confidence intervals] are presented. Quadratic terms for both the IIM and IIV of all sleep variables were tested to be not statistically significant and were thus not included in the final models. In the adjusted models, covariates included: sex (female/male), age, race (white/non-white), education, presence/absence of bed partner, smoking history (current/past/never), perceived stress, and chronic major medical conditions (count); BT = bedtime, RT = risetime, TST = total sleep time, SOL = sleep onset latency, WASO = wake after sleep onset; CAR = cortisol awakening response – linear cortisol slope from awakening till 30 minutes after awakening, Diurnal Slope = linear cortisol slope from 30 minutes after awakening till bedtime; IIM = intraindividual mean, IIV = intraindividual variability; [†]*p* < .10, * *p* < .05, ** *p* < .01.

Table 4

*Results of the IIM and IIV of Actigraphy Sleep Variables Predicting Allostatic Load*

| N = 433 | Unadjusted model | | | Adjusted model | | |
|---|---|---|---|---|---|---|
| | IIM | IIV | $R^2$-IIV | IIM | IIV | $R^2$-IIV |
| BT | 0.15*, .02 | 0.10†, .08 | | 0.12*, .04 | 0.06, .32 | |
| | [0.03, 0.26] | [-0.01, 0.22] | 1.3% | [0.01, 0.23] | [-0.06, 0.17] | 0.5% |
| RT | 0.10†, .07 | 0.09, .13 | | 0.09†, .08 | 0.06, .30 | |
| | [-0.01, 0.21] | [-0.03, 0.21] | 1.0% | [-0.01, 0.20] | [-0.05, 0.18] | 0.5% |
| TST | -0.13*, .02 | 0.09, .14 | | -0.08, .13 | 0.03, .54 | |
| | [-0.24, -0.02] | [-0.03, 0.21] | 1.0% | [-0.19, 0.02] | [-0.08, 0.15] | 0.2% |
| SOL | 0.10†, .097 | 0.14*, .02 | | 0.07, .22 | 0.03, .67 | |
| | [-0.02, 0.23] | [0.02, 0.26] | 2.0% | [-0.04, 0.19] | [-0.09, 0.15] | 0.1% |
| WASO | 0.12†, .07 | 0.13*, .04 | | 0.05, .46 | 0.04, .55 | |
| | [-0.01, 0.25] | [0.01, 0.26] | 1.6% | [-0.08, 0.17] | [-0.09, 0.16] | 0.2% |

*Note.* Standardized coefficients [95% confidence intervals] are presented along with the variance uniquely explained by sleep IIV over and above that of the mean of sleep ($R^2$-IIV). Results are pooled across 50 "imputations" (plausible value imputation for means, IIV, and allostatic load factor scores). Quadratic terms for both the mean and IIV of all sleep variables were tested to be not statistically significant, and were thus not included in the final models. Both the unadjusted and adjusted models had age and sex adjusted. In the adjusted model, the following additional covariates were controlled for: race (white/non-white), smoking history (current/past/never), perceived stress, chronic major medical conditions (count), and allostatic load relevant medications. BT = bedtime, RT = risetime, TST = total sleep time, SOL = sleep onset latency, WASO = wake after sleep onset, IIM = intraindividual mean, IIV = intraindividual variability;

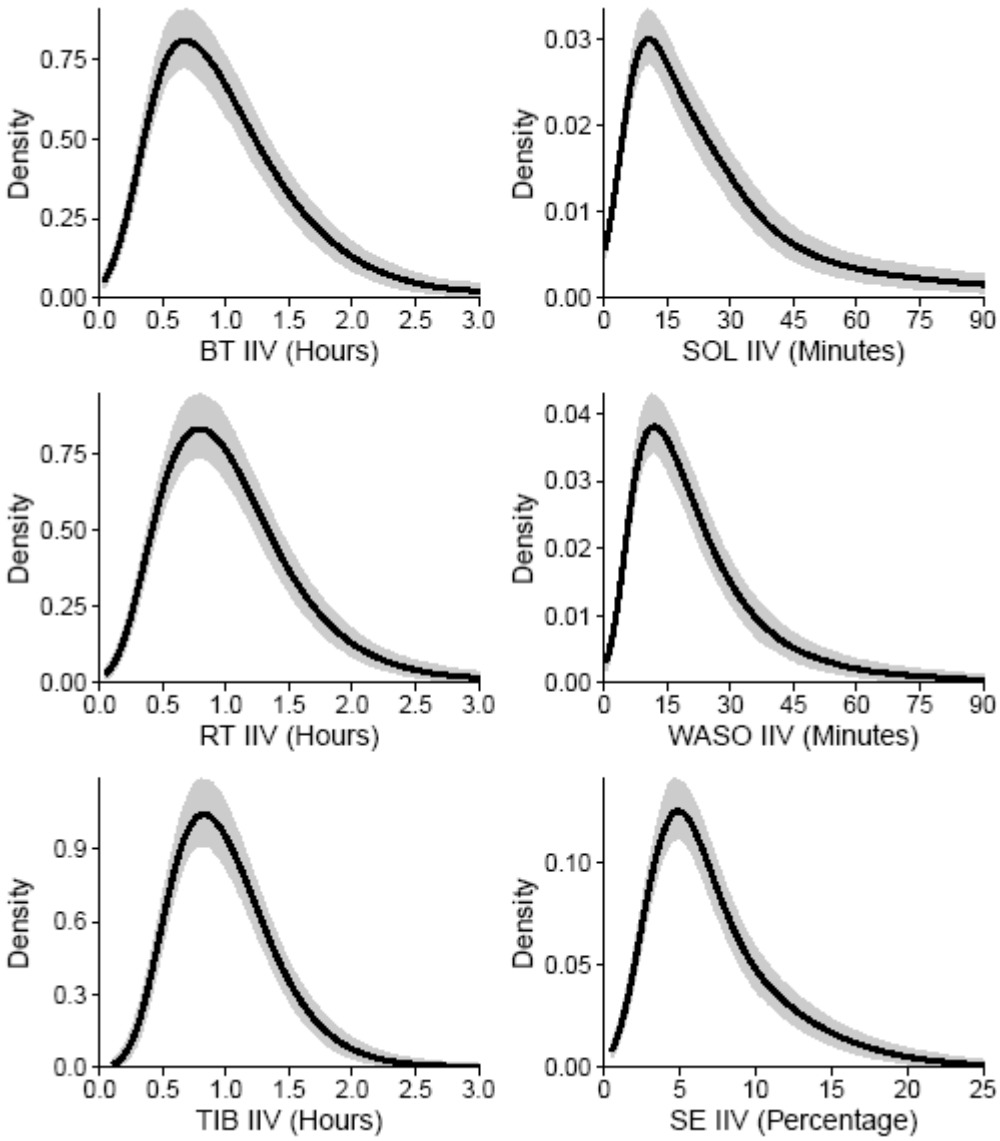† $p < .1$, * $p < .05$, *** $p < .001$.

Figure 1

Figure 2