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SLEEP AND HYPERTENSION (S. JUSTIN THOMAS, SECTION EDITOR)

Variability in Sleep Patterns: an Emerging Risk Factor for Hypertension

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Abstract

Purpose of Review In this review, we summarize recent epidemiological data (2014–2019) that examine the association of sleep variability with blood pressure (BP), discuss potential underlying mechanisms, and highlight future research directions.

Recent Findings Higher standard deviations of sleep duration and sleep-onset timing were not related to BP. However, a higher Sleep Regularity Index score was associated with lower odds of hypertension. Studies on social jetlag, a prevalent form of sleep variability, reported null associations. In contrast, lower interdaily stability in circadian rest-activity rhythms, a measure of invariability in sleep-wake cycles between days and synchronization to light and dark cycles, was associated with higher BP and greater hypertension odds, particularly among non-shift workers.

Summary Sleep variability is consistently associated with risk factors for hypertension. Evidence on sleep variability and BP is limited and varies depending on the measure used to characterize day-to-day variability in sleep. Studies that identify and utilize a standard definition of sleep variability, incorporate a 24-h ambulatory BP monitoring, and ensure coinciding timing of sleep and BP measurements are necessary to disentangle these relationships.

Keywords Sleep variability · Social jetlag · Interdaily stability · Blood pressure · Hypertension

Introduction

Hypertension is one of the most prevalent causes of cardiovascular disease (CVD) that is preventable through a combination of lifestyle behaviors [1••]. One such preventable behavior, poor sleep, is increasingly recognized as a risk factor for elevated blood pressure (BP) and hypertension [2••]. Sleep duration is the most widely studied aspect of sleep health, and both short and long sleep are associated with risk of having elevated blood pressure [2••,3••]. In addition, several other sleep phenotypes such as sleep-disordered breathing, poor sleep quality (including low sleep efficiency and high sleep fragmentation), and insomnia have been linked to hypertension [2••,4,5].

Along with sleep duration and quality and sleep-disordered breathing, accumulating evidence suggests that the stability of sleep-wake cycles may also be associated with CVD risk. The variability of sleep patterns, particularly duration and timing of sleep, could disrupt the circadian rhythmicity of biological processes. Disrupted circadian rhythms play a documented role in elevating cardiovascular risk, as demonstrated initially in studies of shift workers [6]. However, even mild variability in sleep-wake patterns across multiple days, independent of the short sleep duration and circadian misalignment often experienced

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by night shift workers, could lead to circadian disruption and elevate CVD risk [7•,8]. A prevalent form of circadian disruption resulting from differences in sleep duration and timing on workdays versus non-workdays is the phenomenon of "social jetlag." Social jetlag is defined as the desynchrony between circadian and social clocks and is typically assessed by evaluating the difference between weekday and weekend sleep-wake cycles [9, 10]. Several epidemiological studies have shown an association between social jetlag and cardiometabolic health, including BP [11].

The study of associations between measures of sleep variability and BP is in the nascent stages. In light of a growing interest in the role of sleep variability in hypertension etiology, the purpose of the present review is to summarize and discuss studies from the past 5 years (2014–2019) that have examined measures of day-to-day variability in sleep patterns, including studies of social jetlag (defined in Table 1), in relation to hypertension risk and BP level among adults. We also review the evidence on sleep variability in relation to clinical and lifestyle risk factors for hypertension. We conclude by identifying promising lines of research in this area. Notably, discussion of shift work in relation to BP is beyond the scope of this review since the impact of variability in sleep patterns, relative to short sleep duration and circadian misalignment, would be difficult to isolate. To our knowledge, this represents the first review of the epidemiologic evidence on sleep variability, social jet lag, and BP, and we use these data to emphasize clinical and public health implications of the existing literature on this topic.

Associations of Day-to-Day Variability in Sleep Duration and Timing With Blood Pressure and Hypertension Risk

The use of standard deviations (SD) of sleep duration and sleep-onset timing, assessed across multiple nights, has emerged as a means of quantifying day-to-day variability in sleep patterns; higher SD represent greater variability in sleep patterns. We identified two studies that used this approach to investigate the association of sleep variability with BP level and hypertension risk (Table 2). The first of these studies was conducted among 2003 men and women from the Multi-Ethnic Study of Atherosclerosis (MESA) Sleep Ancillary Study, which coincided with MESA clinical Exam 5. This study included cross-sectional and prospective analyses of associations between sleep variability and components of the metabolic syndrome, including BP. Wrist-worn actigraphy was used to assess sleep over a 7-day period. BP and hypertension status were evaluated at clinical Exams 5 and 6 (2010–2011 and 2016–2018, respectively). In both cross-sectional and prospective analyses, higher SD for sleep duration and sleep-onset timing, indicative of greater sleep variability, were

Table 1 Definitions of different measures related to sleep-wake variability

Sleep variability measure	Operational definition	Measurement tool	Reference number for studies using measure
Standard deviation of sleep duration	Standard deviation of nightly sleep duration across the total number of days assessed Higher values indicate greater variability of night-to-night sleep duration	Wrist-worn actigraphy[1]	[12••,13•]
Standard deviation of sleep-onset timing	Standard deviation of nightly sleep onset timing across the total number of days assessed Higher values indicate greater variability of night-to-night sleep onset timing	Wrist-worn actigraphy[1]	[12••]
Sleep Regularity Index	The probability of the same sleep/wake state being observed at any two time points, 24-h apart (30-s epochs) Higher values indicate greater regularity of sleep patterns	Wrist-worn actigraphy	[15•]
Interdaily Stability Index	Days are divided into 24 1-h bins; variance in activity explained by these bins is compared to the total variance across days Scores are between 0 and 1 with lower scores indicating less stability across days	Wrist-worn actigraphy	[7•,8]
Social jetlag	Difference in sleep patterns on work vs. non-workdays, measured by evaluating difference is sleep midpoint (midpoint between sleep onset and sleep offset) on weekdays vs. weekends	Wrist-worn actigraphy or self-reported wake and sleep times on weekdays and weekends	[7•,18–20]

[1] SD of sleep parameters could also be calculated from multi-day self-reported sleep data, although not done in these studies

Table 2 Summary of studies assessing the relationship between measures of sleep-wake variability and blood pressure[1]

Author year (reference)	Cohort and participant characteristics	Study design	Sleep variability measures	Risk estimates	Conclusions
Standard deviation of sleep duration and sleep-onset timing					
Huang & Redline 2019 [12••]	2003 middle-aged to older US men and women from the Multi-Ethnic Study of Atherosclerosis ($n = 970$ for prospective analysis) Mean age at baseline: 69 y	Cross-sectional and prospective analyses (median F/U: 6.3 y) *Exposure:* Actigraph watch worn for 7 d (Exam 5) *Outcome:* BP data collected at Exams 5 and 6 - Hypertension defined as SBP/DBP ≥ 130/85 mmHg	SD of sleep duration categories: < 60 min, 61–90 min, 91–120 min, > 120 min SD of sleep onset timing categories: < 60 min, 61–90 min m, > 90 min	*Cross-sectional* OR (95% CI) of high BP for 1-h increase in SD of duration: 1.10 (0.94–1.29) OR (95% CI) of high BP for 1-h increase in SD of sleep onset timing: 1.08 (0.91–1.28) *Prospective* OR (95% CI) of high BP for 1-h increase in SD of duration: 0.84 (0.60–1.19) OR (95% CI) of high BP for 1-h increase in SD of sleep onset timing: 0.99 (0.70–1.42)	Greater variability in day-to-day sleep duration and sleep onset timing was associated with higher risk of metabolic syndrome but not hypertension
Hausler et al. 2019 [13•]	2598 middle- and older-aged men and women from the CoLaus (Swiss) prospective study of determinants of CVD Mean age for no hypertension vs. hypertension: 59.0 vs. 65.7 y	Cross-sectional analysis *Exposure:* Actigraph watch worn for 14 d *Outcome:* BP data collected at second follow-up - Hypertension defined as SBP/DBP ≥ 140/90 mmHg or use of anti-hypertensive medication	SD of sleep duration across nights *Sleep variability was assessed using two other measures. - *Range of short to long sleep*: The range of sleep duration over the 14 nights - *Weekday/weekend range*: Absolute value of range between average weekday and weekend sleep durations	Sleep variability in min based on hypertension status (Yes vs. No): 63 ± 32 vs. 61 ± 33, $P = 0.18$ OR (95% CI) of hypertension for 1st vs. 4th quartile of sleep duration SD: 1.03 (0.80–1.31)	No association of any of the three sleep variability measures with hypertension status or BP
Sleep Regularity Index					
Lunsford-Avery et al. 2018 [15•]	1976 middle-aged to older US men and women from the Multi-Ethnic Study of Atherosclerosis Mean age: 68.7 y	Cross-sectional analysis *Exposure:* Actigraph watch worn for 7 d *Outcome:* BP data collected at Exam 5 (2010–2012) Hypertension defined as use of anti-hypertensive medication	SRI categories: irregular (1st quintile) vs. regular (5th quintile)	Median (IQR) of SBP (mm Hg) for irregular vs. regular: 121.5 (26.0) vs. 117.0 (24.5), $P = 0.0004$ Median (IQR) of DBP (mm Hg) for irregular vs. regular: 68.5 (14.9) vs. 66.5 (12.0), $P = 0.0061$	Compared to those without hypertension, Sleep Regularity Index was higher in individuals with hypertension. When comparing regular vs. irregular sleepers, trend towards higher rates of hypertension in irregular sleepers
Interdaily Stability Index					
Abbott et al. 2019 [7•]	2156 US Hispanic/Latino men and women from the Sueno Ancillary Study of the Hispanic Community Health Study/Study of Latinos Mean age: 47 y	Cross-sectional analysis *Exposure:* Actigraph watch worn for 7 d *Outcome:* BP collected at baseline visit (30 months before sleep visit) Hypertension defined as use of anti-hypertensive medication	ISI analyzed as a continuous variable	OR (95% CI) of hypertension prevalence per 10% change: − 3.0 (− 5.3 to − 0.6) OR (95% CI) of high SBP per 10% change: − 0.78 (− 1.45 to − 0.12) OR (95% CI) of high DBP per 10% change: − 0.80 (− 1.32 to − 0.28)	Individuals with hypertension had lower interdaily stability Higher interdaily stability was associated with higher SBP, DBP, and with hypertension Associations attenuated after adjustment for income, acculturation, education,

Table 2 (continued)

Author year (reference)	Cohort and participant characteristics	Study design	Sleep variability measures	Risk estimates	Conclusions
					sleep duration, and Apnea-Hypopnea Index Associations did not remain significant after adding shift work to the model When stratified by shift work, associations were significant in non-shift workers only
Sohail et al. 2016 [8]	1137 US men and women from the Rush Memory and Aging Project ($n = 497$ not taking anti-hypertensive meds for subgroup analysis) Mean age: 81.6 y	Cross-sectional analysis *Exposure:* Actigraph watch worn for 7 d *Outcome:* BP measured - Hypertension defined as use of anti-hypertensive medication/AHA criteria	ISI analyzed as a continuous variable	OR (95% CI) of hypertension with 1 SD increase in ISI: 0.80 (0.66–0.98) Estimate (SE) of SBP with 1 SD increase in ISI: − 1.75 (0.89), $P = 0.05$ Estimate (SE) of DBP with 1 SD increase in ISI: − 1.22 (0.51), $P = 0.017$	Higher interdaily stability was associated with lower likelihood of hypertension In non-hypertensive participants, higher interdaily stability was related to lower DBP and SBP
Social jetlag					
Abbott et al. 2019 [7•]	2156 US Hispanic/Latino men and women of descent from the Sueno Ancillary Study (subsample of the Hispanic Community Health Study/Study of Latinos) Mean age: 47 y	Cross-sectional design *Exposure:* Actigraph watch worn for 7 d *Outcome:* BP collected at baseline visit (30 months before sleep visit) Hypertension defined as use of anti-hypertensive medication	Social jet lag was defined as the difference between the mid-sleep point on weekdays and weekends Associations were evaluated per additional hour of social jetlag	Hypertension prevalence (%): − 0.52 (− 3.49 to 2.45) SBP (mmHg): − 0.05 (− 0.71 to 0.62) DBP (mmHg): 0.14 (− 0.39 to 0.68)	No association between social jet lag and BP level
McMahon et al. 2019 [20]	390 healthy US adults Age: 21–35 y	Prospective design *Exposure:* Armband sensor (SenseWear® Mini Armband) for 6–10 d *Outcome:* Resting BP assessed every 6 months over a 2-y period	Social jet lag was defined as the difference between unadjusted midpoints of sleep on a weekend and week day Absolute values of social jet lag (continuous scale) were used for all analyses	Odds of SBP ≥ 120 mmHg per 1-h increase in social jetlag: 1.12 (0.95–1.31) Odds of DBP ≥ 80 mmHg per 1-h increase in social jetlag: 1.02 (0.86–1.21)	No association between social jet lag and hypertension risk
Mota et al. 2017 [18]	792 Brazilian patients with history of chronic disease (obesity, systemic arterial hypertension, type 2 diabetes mellitus, or dyslipidemia) Mean age: 56 y (range 20 to 80 y)	Cross-sectional design *Exposure:* Self-reported sleep and wake times on weekends and weekdays were used to compute sleep midpoint *Outcome:* BP was measured at clinic visit	Social jetlag was calculated as the absolute difference between mid-sleep time on weekends and weekdays, ascertained from self-reported bedtimes and wake times on weekends and weekdays	Increase in BP per 1-h increase in social jet lag: SBP (mmHg) $B = 0.01$, $P = 0.65$ DBP (mmHg) $B = 0.01$, $P = 0.91$	No association between social jet lag and BP level
Rutters et al. 2014 [19]	145 healthy Dutch adults Age: 18–55 y	Cross-sectional design *Exposure:* Adapted version of the Munich Chronotype Questionnaire, which questions typical	Social jetlag was computed from self-reported sleep and wake times as the difference in sleep midpoint between weekdays and weekends/free days	SBP for ≤ 1 h vs. 1 h vs. ≥ 2 h of social jetlag: 126 vs. 128 vs. 124 mmHg P value = 0.35	No association between social jetlag and BP levels

Table 2 (continued)

Author year (reference)	Cohort and participant characteristics	Study design	Sleep variability measures	Risk estimates	Conclusions
		bedtimes and wake times on weekdays and weekends *Outcome:* Resting BP measured at the end of the test day, at approximately 1300 h (average of 2 measurements)	Participants with ≤1 h of social jetlag were compared to those with 1 h or ≥ 2 h of social jetlag	DBP for ≤ 1 h vs. 1 h vs. ≥ 2 h of social jetlag: 75 vs. 77 vs. 78 mmHg *P* value = 0.66	

[1] BP, blood pressure; CI, confidence interval OR; DBP, diastolic blood pressure; ISI, Interdaily Stability Index; odds ratio; SBP, systolic blood pressure; SD, standard deviation; SRI, Sleep Regularity Index

not significantly associated with systolic BP (SBP), diastolic BP (DBP), or hypertension risk. Every 1-h increase in the SD of sleep duration and sleep-onset timing was associated with a non-significant 16 and 7% respective increase in risk for incident hypertension [12••]. These findings were confirmed in an analysis of sleep and cardiovascular risk in 2598 Swiss middle-aged participants from the CoLaus study [13•]. Sleep was measured objectively over 2 weeks via a wrist-worn accelerometer as an optional measure coinciding with the second follow-up visit; variability in sleep duration was defined as the SD of sleep duration across nights. In that study, there was no significant association between sleep duration variability and odds of having hypertension [13•].

Another indicator of day-to-day variability in sleep is the Sleep Regularity Index (SRI) [14,15•]. The SRI uses accelerometry to indicate the likelihood that the same points in time, 24 h apart, fall within the same sleep-wake state [14,15•]. The SRI differs from SD of sleep duration and timing in that it is sensitive to acute changes in sleep patterns. In addition, it considers multiple sleep periods in a single day. This metric was used to evaluate the association between sleep variability and 10-year CVD risk in an ethnically diverse cohort of 1978 adults from the MESA Sleep Ancillary Study [15•]. Compared to those without hypertension, those with hypertension had lower SRI (medians, 72.9 vs. 76.8), which is indicative of greater variability in sleep-wake patterns. Furthermore, compared to irregular sleepers (those in the lowest quintile of SRI), regular sleepers (highest quintile of SRI) had lower SBP and DBP [median (IQR) for SBP, 117.0 (24.5) vs. 121.5 (26.0) mmHg; median (IQR) for DBP, 66.5 (12.0) vs. 68.5 (14.9) mmHg] along with lower rates of hypertension (~ 10 vs. ~ 30%). Contrary to previous findings from this cohort, these data indicate that regularity in sleep patterns may indeed be associated with lower hypertension risk. The difference in findings may be due to the type of measures used, suggesting that more sensitive measures of sleep variability are needed to detect these associations. Determination of the most reliable methodology to capture sleep variability is needed. Alternatively, the regularity in sleep timing, which is captured by the SRI, is more strongly associated with BP and hypertension risk than consistency in sleep duration.

Association of Interdaily Stability in Circadian Rest-Activity Rhythms With Blood Pressure

The Interdaily Stability Index (ISI) is one of the variables used to assess the circadian pattern of rest-activity rhythms. The ISI is estimated from accelerometry count data, collected over several days, using rhythmometric methods, and serves as a non-parametric measure of invariability between days and synchronization to environmental cues [16•]. In two recent studies (Table 2), the ISI has been used to quantify the

regularity of sleep patterns over the course of several days and to provide a measure of sleep-wake rhythms stability in relation to BP [7•,8].

Analysis of interdaily stability and hypertension risk in 2156 men and women from the Hispanic Community Health Study/Study of Latinos (HCHS/SOL) Study showed significant associations of ISI with both BP levels and hypertension prevalence [7•]. Small but statistically significant differences in ISI were observed between participants with and without hypertension; those without hypertension had higher scores, indicative of greater stability of rest-activity patterns across days. In addition, a 10% decline in interdaily stability was related to a 3% increase in hypertension prevalence (95% CI, 0.6–5.3). A 10% reduction in ISI score was also associated with significant increases in SBP and DBP of 0.78 mmHg (95% CI, 0.12–1.45) and 0.80 mmHg (95% CI, 0.28–1.32), respectively, although the clinical relevance of these changes in BP levels is unclear. These associations were attenuated after adjustment for other factors, including shift work; however, analyses stratified by shift work status showed that associations between interdaily stability and hypertension remained significant in the non-shift work group [7•]. In the Rush Memory and Aging Project, a study conducted among 1137 men and women aged 81.6 ± 7.5 years, greater interdaily stability (higher ISI) was associated with 22% lower odds of hypertension [8]. This association was independent of differences in objectively measured total daily physical activity or rest. Taken together, these findings suggest that the stability of sleep-wake or rest-activity patterns is associated with hypertension risk at the population level.

Social Jetlag and Blood Pressure

While SD of sleep duration and sleep-onset timing, SRI, and ISI provide important insight on variability in sleep and rest-activity patterns, a pervasive phenomenon related to sleep variability is social jetlag. Social jetlag reflects a persistent misalignment between an individual's endogenous circadian clock and their actual sleep and wake times as a consequence of modern society's work and social schedules [11]. Individuals cycle back and forth between socially imposed sleep-wake schedules on workdays and sleep-wake schedules that reflect innate circadian rhythms on non-workdays. Given that social jetlag represents the difference in sleep patterns on workdays vs. non-workdays, it may also serve as an indicator of variability in habitual sleep patterns. Although there are no formal estimates from epidemiological studies on the actual prevalence of social jetlag in the US population, recent internet-based studies indicate that more than two-thirds of participants report at least 1 h of social jetlag [9, 10], suggesting that this phenomenon is highly prevalent worldwide. In Australia, one-third (31.1%) of respondents experienced > 1 h of social jetlag [17], whereas its prevalence was estimated at 24% in Brazil [18]. In one Dutch study, approximately 63% of participants reported > 1 h of social jetlag [19].

Four studies have examined social jetlag, defined as the difference between the midpoint of sleep on weekdays and weekends, in relation to BP and have demonstrated null associations (Table 2) [7•,18–20]. In the HCHS/SOL study, there was no association between social jetlag and BP or hypertension risk [7•]. A prospective study of 390 young and healthy US adults quantified social jetlag from rest-activity monitoring (armband actigraphy) over 6–10 days every 6 months for a period of 2 years [20]. Social jetlag was not independently associated with SBP or DBP nor was it associated with anthropometric measures. Similarly, in a cross-sectional study of 792 Brazilian adults with obesity, hypertension, type 2 diabetes, and/or dyslipidemia, an absolute difference between mid-sleep time on weekends and weekdays of ≥ 1 h was not associated with BP [18]. However, social jetlag was associated with greater risk of having overweight/obesity in all participants and poorer lipid profiles (e.g., higher triglycerides and total cholesterol) among the metabolically unhealthy obese participants.

Null associations of social jetlag with hypertension risk were also observed in an observational study of 145 healthy participants (67 men and 78 women; age, 18–55 years; BMI, 18–35 kg/m^2) from the Netherlands [19]. Although the participants with ≥ 2 h of social jetlag had shorter sleep duration during the week and were more physically inactive compared with participants who had ≤ 1 h of social jetlag, there was no significant association with BP or with measures of adiposity (BMI and waist circumference) [19]. Thus, social jetlag is associated with increased body weight and cholesterol, physical inactivity, and shorter sleep duration, suggesting its role as a cardiometabolic risk factor.

Associations of Sleep Variability With Risk Factors for Hypertension: Mechanisms Underlying a Possible Sleep Variability-BP Link?

Even though the limited existing epidemiological evidence on day-to-day variability in sleep duration, sleep timing, and social jetlag in relation to BP is inconsistent, such relationships are biologically plausible. Both day-to-day variability in sleep patterns and social jetlag have been linked to increased risk of having the metabolic syndrome [12••,15•,21,22•] as well as known clinical and lifestyle risk factors for hypertension including obesity, insulin resistance, and diet.

Measures of sleep variability are associated with obesity, a risk factor for the development of hypertension [23] that is estimated to explain up to 70% of hypertension cases [24]. In a population of older US men and women (Osteoporotic

Fractures in Men Study/Study of Osteoporotic Fractures), each 1-h increase in actigraphy-assessed SD in sleep duration was associated with 63% and 22% higher likelihood of obesity in men and women, respectively [25]. Similar findings of an association between sleep duration variability and BMI were observed in the Hiroshima Sleep and Healthcare study; this cross-sectional analysis of nearly 10,000 adults defined sleep variability as the difference between longest and shortest self-reported sleep duration in a night over the course of a week [26]. Lower variability in day-to-day sleep duration was also correlated with greater reductions in BMI at the 1-year time point of the PREDIMED-Plus Trial, suggesting that sleep stability may contribute to success in weight loss [27•].

Beyond variability in sleep duration, instability in sleep timing has also been linked to obesity [12••,28]. In an investigation of sleep variability in relation to metabolic syndrome in MESA, higher SD of actigraphy-assessed sleep-onset timing was associated with 25% higher odds of having central obesity [12••]. Variability in self-reported bedtime, measured using the Sleep Timing Questionnaire [29], was also associated with increased likelihood of obesity in a sample of 225 US adults recruited at an urban hospital-affiliated family medicine center [28]. Similarly, social jetlag is related to obese phenotypes, including higher average BMI, obesity risk, and fat mass, in the Dunedin Multidisciplinary Health and Development Study ($n = 1037$) [21]. In addition, social jetlag, over and above the impact of sleep duration, was also related to higher BMI and greater likelihood of being overweight in a sample of 65,000 respondents from a European online database [10].

Factors downstream of obesity, including insulin resistance and inflammation, are also related to BP levels [23]. Indeed, sleep variability has been linked to markers of glycemic regulation and inflammation in the literature. Sleep variability, including lower SRI scores, higher SD of sleep duration and sleep-onset timing, and social jetlag are associated with higher fasting blood glucose and glycated hemoglobin levels as well as higher homeostatic model assessment insulin resistance values [12••,15•,18,30,31]. Social jetlag is associated with increased risk for prediabetes and type 2 diabetes [22•]. A cross-sectional analysis showed that social jetlag of 1–2 h was associated with 73% greater likelihood of prediabetes (fasting plasma glucose ≥ 6.1 mmol/L and HbA1c ≥ 6.0%) and type 2 diabetes (fasting plasma glucose levels ≥ 6.5 mmol/L, HbA1c levels ≥ 6.5%) in younger but not in older adults [22•]. Observed associations of sleep variability and social jetlag with markers of diabetes are noteworthy, given that the presence of type 2 diabetes can lead to the development of hypertension [32]. Likewise, day-to-day variability in self-reported time in bed and social jet lag are both associated with markers of inflammation, including interleukin-6 [33] and cortisol [19], which are linked to increased BP [34, 35]. Taken together, these data suggest that variability in sleep duration and timing as well as social jetlag could contribute to hypertension risk, possibly via changes in insulin sensitivity and inflammation.

Finally, variability in sleep patterns appears to have a detrimental influence on diet, one of the most important behavioral risk factors for hypertension [1••]. In the HCHS/SOL, variability in sleep duration (assessed using the SD of sleep duration measured over several nights) was inversely related to intake of whole fruits [36]. Furthermore, among Brazilian adults, social jetlag (> 1 h) was associated with higher reported intakes of total calories, protein, total fat, saturated fat, cholesterol, and servings of meat and eggs and sweets [37]. In addition to poor diet quality, social jetlag was also related to unhealthy eating patterns, including later meal times [37]. Later circadian timing of food intake has in turn been recently linked to higher BP levels and greater odds for hypertension [38]. Thus, diet may represent an additional mechanism through which social jetlag may influence blood pressure levels.

In summary, epidemiologic studies support associations of sleep variability with health outcomes strongly predictive of hypertension risk, including obesity, glucose dysregulation, and inflammation. While causal pathways remain to be established, these observations suggest a link between variable sleep patterns and vascular health.

Future Research Directions

Heterogeneity in the sleep variability metrics, the definitions of hypertension, methods to assess BP, and characteristics of study populations across available studies limit comparability of results. Perhaps the most notable limitation is the lack of a standard definition for the construct of sleep variability. Measures, such as SD of sleep duration and sleep-onset timing, indices like the SRI and ISI, and social jetlag, may reflect different aspects of sleep variability. Alternatively, it may be useful to use these measures in combination, as they may capture distinct aspects of sleep variability that exhibit differential associations with BP, which may be important to decipher. Given that an increasing number of population-based cohort studies have ancillary sleep studies with objectively assessed sleep, this could be a useful source for identification of standardized metrics to assess sleep variability. In the future, clinical trials that randomly allocate variable bedtimes and sleep duration are needed to establish a definitive link between sleep patterns and BP and to identify novel interventions targeting sleep that improve cardiovascular health.

In addition, standardizing timing and the method of BP assessment relative to the sleep assessment is needed. In some epidemiological studies, such as MESA and HCHS/SOL, clinic BP is assessed at the main study exam, and sleep is assessed at a different time point during the ancillary sleep study [7•,12••,15•]. It is possible that the observed null

associations are due to the lack of concurrent sleep and BP assessments. Furthermore, there is a circadian rhythmicity to BP levels [39] that cannot be captured during a clinic BP assessment, and abnormalities in 24-h BP diurnal patterns are associated with elevated cardiovascular risk, independent of clinic BP levels. In fact, recent data suggest that nocturnal BP may be a stronger predictor of CVD risk than clinic BP [40•]. Incorporating 24-h ambulatory BP monitoring concurrently with wrist actigraphy in population-based cohort studies could be useful to better assess how day-to-day variability of sleep patterns influences morning BP surge, nocturnal dipping, and night-to-day variability in BP.

Finally, a key opportunity to extend knowledge on the role of sleep variability in the development of hypertension would be to examine these associations in diverse and vulnerable populations. For instance, social jetlag should be evaluated in relation to BP among racial/ethnic minorities, particularly African Americans, who may be more prone to disrupted sleep [41, 42] and are disproportionately affected by hypertension [43]. Although sleep variability in relation to BP has been investigated in a subset of MESA and HCHS/SOL participants, these studies do not evaluate differences in these associations by sex, age group, or by race/ethnicity due to sample size limitations.

Conclusions

Intra-individual variability in habitual sleep patterns, including irregular sleep-onset timing and duration across days, as well as social jetlag, appears to contribute to poor cardiometabolic health. Variability in sleep timing is more consistently associated with BP than variability in sleep duration. Furthermore, while social jetlag is not associated with BP, interdaily stability in sleep-wake cycles and rest-activity rhythms has been associated with higher hypertension risk. The inconsistency of these associations may be due to the limited epidemiologic data on this topic, particularly from prospective studies, differences in study populations, as well as methodological limitations.

Standardization of metrics to assess sleep variability and the use of continuous BP monitoring, which allows capturing of diurnal and nocturnal variations in BP levels, are needed to accurately assess the link between sleep patterns and cardiovascular health. Of greatest importance is the necessity to develop a standardized definition of sleep variability to facilitate comparisons across different studies and populations. We suggest focusing on variability in sleep duration and sleep-onset timing in future research, as these represent modifiable behavioral factors that could easily be targeted for intervention. Such studies would be critical for disentangling the complex relations between sleep variability and BP and for the development of public health guidelines and clinical recommendations addressing sleep schedules to optimize BP control.

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Compliance With Ethics Guidelines

Conflict of Interest The authors declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

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