



# The Emerging Importance of Sleep Regularity on Cardiovascular Health and Cognitive Impairment in Older Adults: A Review of the Literature

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**Abstract:** The regularity of sleep/wake patterns across multiple days is emerging as an important determinant of health. However, the association between sleep regularity and health outcomes in the aging population is not well understood. The current systematic review identified 22 publications that examined the relationship between sleep regularity and selected health outcomes: cardiovascular risk, cognitive impairment, and mortality. All studies were published after 2010, reflecting a growing research interest in daily sleep regularity. Low sleep regularity was consistently associated with higher cardiovascular risk and elevated risk of all-cause mortality. Results on cognitive impairment are mixed, with inconsistency likely attributed to small sample sizes and differences in sleep regularity assessment. Overall, regularity in sleep carries important information about health and should be included in future studies that collect daily sleep measures. Gaps in literature and methodological shortcomings are discussed.

**Keywords:** sleep regularity, Aging, cardiovascular health, cognitive impairment, mortality

It is widely acknowledged that advancing age brings about changes in both the duration and quality of sleep.<sup>1</sup> These age-related differences are systematically related to cardiovascular health,<sup>2</sup> cognitive abilities,<sup>3</sup> dementia,<sup>4</sup> and all-cause mortality.<sup>5</sup> Most existing literature on sleep and health outcomes has largely focused on single-night assessment of sleep duration and efficiency. However, no two nights of sleep are the same, and the day-to-day variations in sleep metrics can carry additional information about a person's health compared to average measures.

The day-to-day variation in sleep/wake patterns sleep metrics (ie duration and bedtime) over an observation period has been reported across a wide age range.<sup>6</sup> This variation, also known as sleep regularity, has been linked to health-relevant factors such as mental well-being and physical illness.<sup>7-9</sup> Sleep regularity can be quantified as the intra-individual standard deviations of sleep metrics across days (duration, bedtime and fragmentation) or as similarity in sleep/wake patterns across 24 hours (sleep regularity index).<sup>10</sup> Wrist actigraphy and other wearable devices have made it feasible to objectively assess daily sleep regularity at scale and over periods of weeks and longer, offering a richer understanding of sleep's relationship with health.

A comprehensive review<sup>11</sup> by Bei et al in 2016 identified 53 publications examining the correlates of sleep regularity across the lifespan. The review found that low sleep regularity, despite imperfect assessments, was associated with adverse health outcomes. Although most studies in the Bei et al, review appear not to be explicitly designed to evaluate sleep regularity, over a third (19) of the studies included older adults over the age of 50, indicating a substantial interest in examining the relationship between sleep and health outcomes in this age group.

The current review will specifically focus on sleep regularity in older adults over the age of 50. The declines in both physical and cognitive health that come with aging, leading to premature mortality, impose substantial costs on both healthcare and public service systems. Various measures of sleep have been examined as potential biomarkers in aging.<sup>12,13</sup> In the 2016 review by Bei et al, cardiovascular risk and cognitive impairment/dementia were the two most

studied outcomes in older adults. The current review would explicitly focus on these two health outcomes with the most evidence and the ultimate health outcome (premature mortality).

Recent large-scale epidemiological studies, integrating actigraphy for objective sleep measurement, have paved the way for more in-depth investigations into how sleep regularity interacts with important health outcomes. Datasets like MrOS,<sup>14</sup> SOF,<sup>14</sup> MESA,<sup>15</sup> and UK Biobank<sup>16–18</sup> combine multi-night actigraphy-measured sleep with assessments of cardiovascular risk factors, cognitive impairment, and dementia. Some of these datasets, such as UK Biobank, tracked mortality.<sup>16,18</sup> Consequently, there has been a notable increase in publications since the 2016 review focusing on sleep regularity and its implications for health in the aging population.

Considering this emerging research topic, the primary objective of this review is to systematically compile existing evidence regarding the importance of sleep regularity on cardiovascular health, cognitive impairment/dementia, and risk of premature mortality in older adults. After summarizing the available literature, we sought to identify gaps in current knowledge, to guide future research in this area.

## Methods

### Data Sources and Searches

The initial search was done through PubMed and Web of Science, using pre-specified search terms. A filter was applied in all databases to include studies on human adults aged 50 and above.

Included articles met the following requirements: a) measured sleep (ir)regularity, b) include a sample of older adults (average age 50+), c) reported health outcomes including cardiovascular risk factors, cognitive functioning and dementia and incident of mortality and d) reported associations between sleep regularity measures from a) and health measures from c).

The search terms used for PubMed and PsycInfo are combinations of the following terms: “Sleep (ir)regularity” OR “Sleep variability” OR “(ir)regular sleep” OR “variation in sleep” AND “Ageing” OR “Aging” OR “older adults” OR “elderly” OR “senior” NOT “review” NOT “meta-analysis” NOT “sleep deprivation” NOT “sleep apnea” NOT “commentary” NOT “animal”.

### Study Selection

Articles were excluded if they only assessed sleep regularity and health outcomes in: (a) patients with sleep disorders (ie, insomnia and sleep apnea), and (b) lifespan samples of adults without separately reporting results for older adults. Articles were excluded if sleep regularity was associated with other health factors: (a) cardiometabolic diseases (incl. diabetes), (b) mood disorders, and (c) other diseases (incl. COVID-19 infection).

Articles were also excluded if sleep regularity was assessed after sleep manipulation (eg, sleep deprivation experiments or pharmacological trials).

Reference lists of included studies and previous reviews<sup>11,19,20</sup> were also searched.

### Data Extraction

For each study, a series of pre-defined characteristics were systematically extracted: a) year of publication, b) mean age of older participants, c) device used to assess sleep (ir)regularity, d) metrics used to quantify sleep (ir)regularity, e) number of days of sleep recording, f) sample size, and g) availability of data (ie, open databases).

### Definition of Sleep Regularity

Sleep (ir)regularity is defined as the daily variation in sleep/wake pattern. Measures of sleep (ir)regularity include standard deviation and coefficients of variance of sleep metrics (ie, duration, timing, and efficiency), or the sleep regularity index (SRI)<sup>10</sup> which indexes the average concordance in sleep/wake state across two consecutive-24-hour periods. For the current review, all metrics that assess daily variation in sleep/wake patterns were eligible, including self-reported sleep regularity. In the results section, high sleep regularity refers to low standard deviations of sleep metrics or a high sleep regularity index.

## Outcome Measures

Outcomes evaluated were all-cause mortality, cognitive impairment including dementia and cardiovascular risk factors, which were blood pressure (including hypertension), BMI, waist circumference, cardiovascular diseases (including events in the heart and brain), adiposity, and obesity.

## Quality Assessment

We utilized the quality assessment scale adopted by Bei et al in their 2016 systematic review.<sup>11</sup> This assessment scale includes ratings of: 1) A priori aim/hypothesis; 2) Sample size justification; 3) Sample representativeness; 4) Number of days; 5) Quality of sleep measures; 6) Quality of correlates measures; 7) Rates of missing in daily data; 8) Inferences and conclusions. Quality of sleep measures was rated based on the following criteria: a) if a wearable/nearable tracker was used to assess sleep, the device was a research-grade device (eg actigraph) or well-validated commercial device (eg, Fitbit); b) quality control and processing of tracker data followed a standard approach (eg, removal of days with less than 8 hours of recording); c) if a self-report questionnaire was used, it had a question specifically for sleep regularity within the past week/month.

## Results

### Search results

Systematic searches returned 5526 records for title and abstract screening. After initial screening, 119 articles were selected for full-text screening, 22 of which were included for data extraction and review. See [Figure 1](#) for a flowchart of the search process. Characteristics of the included studies are presented in [Table 1](#).

### Context and Design

All included studies were published after 2010. Almost all studies (21 out of 22) were observational. The single intervention study did not target sleep or sleep regularity.<sup>26</sup> Seven studies analyzed sleep and health data from public datasets that are accessible to researchers (MESA, MrOS, SOF, and UK Biobank). In addition, six studies were part (ancillary data) of large-scale epidemiological studies that aimed to examine public health.

### Characteristics of the Samples

Most studies (17 out of 21) were conducted in North America or Europe, three studies were conducted in Japan and one in Korea.

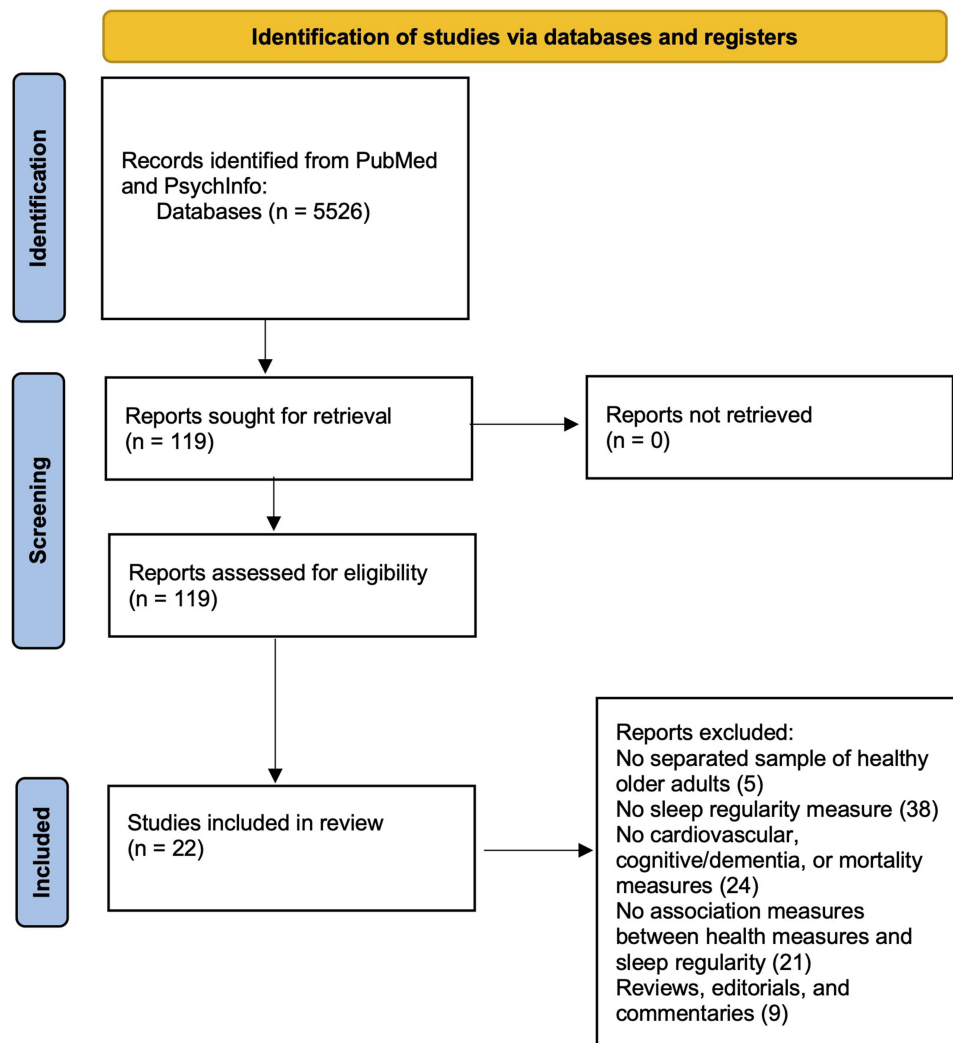
Two studies included older patients with mild cognitive impairment and Alzheimer's disease. The 20 other studies recruited cognitively normal community-dwelling older adults. Thirteen studies have sample sizes over 1000, the other 9 studies have sample sizes under 200. One study<sup>25</sup> included some middle-aged adults, with a mean age of 50. All other studies have mean ages over 55.

### Measurements and Analyses of Sleep Regularity

Seventeen studies used standard deviations of sleep metrics to assess regularity. Three used the SRI. The remaining two studies used participants' self-reported sleep regularity ratings. Eighteen studies used wrist-worn accelerometer-based devices to assess sleep/wake activities. One study used an infrared motion sensor to detect movements in bed. One study used a sleep diary, and two studies used a single question in a sleep questionnaire to assess self-report sleep regularity.

## Quality Assessment

Quality assessment of individual studies is presented in [Table 2](#). Inferences and conclusions from all studies were well supported by results. Most studies recruited representative samples (21 out of 22) and well-validated health outcome measures (21 out of 22). Majority of the studies used well-validated assessment devices for daily sleep/wake patterns (19 out of 22). Most studies have a-prior hypotheses about sleep regularity and health outcomes (14 out of 22). Only 5 studies recorded sleep for more than 7 days, and 2 studies used one-time self-report sleep regularity estimates. None of



**Figure 1** PRISMA Flow chart for the literature search.

the studies provided justification of sample size, although most studies (14) had sample sizes over 200 suggesting sufficient power. No study reported the number of days when data were missing.

## Primary Findings

Of the 22 studies included in the current review, 10 examined associations of sleep regularity with cardiovascular health (including cardiovascular diseases and risk factors). Nine studies examined sleep regularity with cognitive functioning in healthy older adults and with dementia status in patients. The remaining 3 studies examined how sleep (ir)regularity was associated with all-cause mortality.

## Sleep Regularity and Cardiovascular Risk/ Adiposity

The cardiovascular risk factor examined by most studies was body weight ( $N=7$ ). In general, low sleep regularity was related to high BMI, large waist circumference, high body fat, increased fat mass and high likelihood of obesity.<sup>7,14,21,23,24</sup> In a lifestyle intervention study, low baseline sleep regularity was associated with less decrease in weight and BMI in older adults.<sup>26</sup>

Fewer studies examined the likelihood of cardiovascular diseases. Low sleep regularity was related to greater prevalence of hypertension, high systolic and diastolic blood pressures, and high risk of developing cardiovascular

**Table 1** Characteristics of Included Studies

Author Last Name	Age	Device	Measure of Regularity	N Days	Sample N	Open Data	Outcomes	Main Results
Cardiovascular Risk								
Full <sup>15</sup>	68.6	ActiWatch Spectrum	ISDs of sleep duration and sleep timing	7 days	2032	MESA	Cardiovascular risk factors	PR vs ref. group (TST ISD<60 min) <b>Coronary artery calcium (&gt;300):</b> 61<TST ISD<90 PR=1.26; 91<TST ISD<120 PR=1.32; TST ISD>120 PR=1.33 <b>Carotid plaque:</b> 61<TST ISD<90 PR=1.1; 91<TST ISD<120 PR=1.09; TST ISD>120 PR=1.09 <b>Carotid IMT (&gt;0.9):</b> 61<TST ISD<90 PR=0.99; 91<TST ISD<120 PR=0.99; TST ISD>120 PR=1.03 <b>Ankle-brachial Index (&lt;0.9):</b> 61<TST ISD<90 PR=1.5; 91<TST ISD<120 PR=1.62; TST ISD>120 PR=1.75
Häusler <sup>21</sup>	60	GENEActiv	ISD of sleep duration	14 days	2598	No	Obesity and hypertension	OR vs ref (1st quartile TST ISD) <b>Obesity:</b> 2nd quartile OR=1.15 3rd quartile OR=1.22 4th quartile OR=1.44 <b>Hypertension:</b> 2nd quartile OR=1.15 3rd quartile OR=1.22 4th quartile OR=1.44
Huang <sup>22</sup>	68.6	ActiWatch Spectrum	ISDs of sleep duration and sleep timing	7 days	2032	MESA	Incident cardiovascular disease	HazR vs ref <b>TST ISD (ref. TST ISD&lt;60min)</b> 61<TST ISD<90 HazR=1.09; 91<TST ISD<120 HazR=1.59; TST ISD>120 HazR=2.14 <b>SOT ISD (ref. SOT ISD&lt;30min)</b> 31<SOT ISD<60 HazR=1.16; 61<SOT ISD<90 HazR=1.52; SOT ISD>90 HazR=2.11

(Continued)

Table 1 (Continued).

Author Last Name	Age	Device	Measure of Regularity	N Days	Sample N	Open Data	Outcomes	Main Results
Kim <sup>23</sup>	83.4	ActiGraph GT3X+	ISDs of sleep duration and sleep timing	5 nights	191	No	Body fat composition	$\beta$ between ISDs and body composition <b>BMI:</b> Bedtime ISD: $\beta=0.21$ Waketime ISD: $\beta=0.07$ Sleep timing ISD: $\beta=-0.13$ Sleep Duration ISD: $\beta=0.02$ <b>Percentage body fat:</b> Bedtime ISD: $\beta=0.2$ Waketime ISD: $\beta=0.01$ Sleep timing ISD: $\beta=-0.01$ Sleep Duration ISD: $\beta=0.02$ <b>Fat mass index:</b> Bedtime ISD: $\beta=0.23$ Waketime ISD: $\beta=0.03$ Sleep timing ISD: $\beta=-0.06$ Sleep Duration ISD: $\beta=0.02$ <b>Percentage lean mass:</b> Bedtime ISD: $\beta=-0.21$ Waketime ISD: $\beta=0.002$ Sleep timing ISD: $\beta=0.01$ Sleep Duration ISD: $\beta=-0.02$ <b>Lean/fat mass ratio:</b> Bedtime ISD: $\beta=-0.18$ Waketime ISD: $\beta=0.005$ Sleep timing ISD: $\beta=0.02$ Sleep Duration ISD: $\beta=-0.05$
Lunsford-Avery <sup>7</sup>	68.7	ActiWatch Spectrum	Sleep regularity index	7 days	1978	MESA	10-year risk of cardiovascular disease, hypertension and obesity	Pearson' correlations with 10-year risks <b>Cardiovascular disease:</b> $r=-0.13$ <b>BMI:</b> $r= -0.14$
Ogilvie <sup>24</sup>	68.6	ActiWatch Spectrum	ISD of sleep duration	7 days	2146	No	BMI, waist circumference, and body fat	Regression $\beta$ <b>BMI:</b> $\beta=0.23$ <b>Waist circumference:</b> $\beta=0.025$ <b>Total body fat:</b> $\beta=0.014$

Patel <sup>14</sup>	76.4 (M) 83.5 (W)	Sleepwatch-O	ISDs of sleep duration and sleep timing	2 nights	3053 Men 2985 Women	MrOS and SOF	Obesity	OR per hour increase <b>MrOS sleep duration ISD:</b> OR=1.63 <b>MrOS sleep midpoint ISD:</b> OR=1.23 <b>SOF sleep duration:</b> OR=1.22 <b>SOF sleep midpoint:</b> OR=1.32
Parise <sup>25</sup>	50	ActiWatch 2	ISDs of sleep duration and sleep timing	7 days	1720	No	Hypertension	Logistic regression OR <b>Sleep duration ISD:</b> OR=1.004
Papandreou <sup>26</sup>	65	GENEActiv	ISDs of sleep duration and sleep timing	8 days	1986	No	Weight, BMI and waist circumference	Linear regression $\beta$ between ISD sleep and 12-month changes weight BMI and waist circumference. <b>Weight:</b> $\beta=-2.1$ <b>BMI:</b> $-0.7$ <b>Waist circumference:</b> $-2.3$
Sasaki <sup>27</sup>	70	Self-report	Self-report sleep duration variability	N/A	5591	No	Obesity	OR=1.22
Cognitive impairment and Dementia								
André <sup>28</sup>	72	MotionWatch8	ISD of sleep fragmentation index	7 days	66	No	Neuroimaging biomarkers	Negative correlation between sleep fragmentation ISD and grey matter volume in thalamus
Diem <sup>29</sup>	82.6	Sleepwatch-O	ISDs of sleep efficiency, sleep duration, WASO, and sleep latency	3 nights min	1245	MrOS	Risk of incident MCI and dementia	OR vs ref group (1st quartile) <b>Sleep duration ISD:</b> 2nd quartile OR=0.82; 3rd quartile OR=0.98; 4th quartile OR=1.4 <b>Sleep efficiency ISD:</b> 2nd quartile OR=1.89; 3rd quartile OR=1.48; 4th quartile OR=1.92 <b>WASO ISD:</b> 2nd quartile OR=1.29; 3rd quartile OR=1.22; 4th quartile OR=1.25 <b>Sleep latency ISD:</b> 2nd quartile OR=0.98; 3rd quartile OR=0.92; 4th quartile OR=1.37
Fenton <sup>30</sup>	66.4	GENEActiv	ISDs of sleep efficiency and sleep duration	30 days	52	No	Beta- Amyloid burden and cognitive functions	Regression $\beta$ <b>Sleep duration ISD:</b> Amyloid burden $\beta=0.01$ MoCA score $\beta=-0.14$ Inhibitory control $\beta=0.01$ <b>Sleep efficiency ISD:</b> Amyloid burden $\beta=0.03$ MoCA score $\beta=-0.44$ Inhibitory control $\beta=0.02$

(Continued)

Table 1 (Continued).

Author Last Name	Age	Device	Measure of Regularity	N Days	Sample N	Open Data	Outcomes	Main Results
Guarnieri <sup>31</sup>	70.5	Fitbit Flex	Sleep regularity index	7 days	158	No	AD vs MCI vs Control	SRI significantly lower in AD than controls
Hayes <sup>32</sup>	86.9	Infrared motion sensor	ISDs of sleep duration and sleep timing	26 weeks	45	No	MCI status	aMCI had smaller ISD than naMCI
McCrae <sup>33</sup>	70.2	Sleep diary	ISD of sleep duration	14 days	72	No	Cognitive functions	Regression $\beta$ <b>Letter series:</b> TSTsd $\beta=-0.01$ <b>Symbol digit:</b> TSTsd $\beta=-0.02$
Okuda <sup>34</sup>	70.4	Motionlogger	ISD of sleep timing	5 days min	63	No	Cognitive functions	Correlation between sleep timing ISD and total errors on WCST: $r=0.28$
Silva <sup>35</sup>	73.1	MotionWatch8	ISDs of sleep duration, sleep efficiency, and sleep fragmentation	7 days	113	No	Cognitive impairment and cortical thickness	Sleep fragmentation index ISD was negatively associated with cortical thickness in left superior frontal gyrus.
Westerberg <sup>36</sup>	72	Wrist-worn sensor	ISDs of sleep duration, latency, and WASO	14 nights	20	No	Cognitive functions	Correlation between ISDs and Logical Memory <b>TIB ISD:</b> $r=-0.48$ <b>TST ISD:</b> $r=-0.53$ <b>Latency ISD:</b> $r=-0.49$ <b>WASO ISD:</b> $r=-0.5$
Mortality								
Omichi <sup>37</sup>	58	Self-report	Subjective regularity	N/A	81382	No	All-cause mortality	HazR vs ref (6–8 h/day) <6h/day HR=1.03 >8h/day HR=1.06
Wallace <sup>17</sup>	76.4 (M) 83.5 (W)	Sleepwatch-O	ISD of sleep midpoint	4 nights min	2640 Men 2430 Women	MrOS and SOF	All-cause mortality	HazR in men and women <b>Men:</b> Low vs medium ISD: HR=0.98 High vs medium ISD: HR=1.04 High vs low ISD: HR=1.06 <b>Women:</b> Low vs medium ISD: HR=1.01 High vs medium ISD: HR=1.2 High vs low ISD: HR=1.19
Windred <sup>18</sup>	62.8	ActiWatch	Sleep regularity index	7 days	60,977	UK Biobank	All-cause mortality	HazR vs ref group (SRI 0–20%) SRI 20–40% HR=0.8 SRI 40–60% HR=0.75 SRI 60–80% HR=0.72 SRI 80–100% HR=0.7

**Note:** Studies are ordered alphabetically based on the last names of the first authors.

**Abbreviations:** ISD, intraindividual standard deviation; MESA, Multi-Ethnic Study of Atherosclerosis; MrOS, The Osteoporotic Fractures in Men Sleep Study; SOF, Study of Osteoporotic Fractures; N days, number of days from which sleep data was recorded, TST, total sleep time; SOT, sleep onset time; TIB, time in bed; WASO, wake after sleep onset; PR, prevalence ratio; OR, odds ratio; HazR, hazards ratio.



**Table 2** Quality Assessment of Included Studies

	A Prior Aim/ Hypothesis	Sample Size Justification	Sample Representativeness	Number of Days	Quality of Sleep Measures	Quality of Correlates Measures	Rates of Missing in Daily Data	Inferences and Conclusions
Andre <sup>28</sup>	-	-	+	7	+	+	-	+
Diem <sup>29</sup>	-	-	+	7	+	+	-	+
Fenton <sup>30</sup>	+	-	+	30	+	+	-	+
Full <sup>15</sup>	+	-	+	7	+	+	-	+
Guarnieri <sup>31</sup>	-	-	+	7	+	+	-	+
Hausler <sup>21</sup>	+	-	-	14	+	+	-	+
Hayes <sup>32</sup>	+	-	+	26	-	+	-	+
Huang <sup>22</sup>	+	-	+	7	+	+	-	+
Kim <sup>23</sup>	+	-	+	5	+	+	-	+
Lunsford- Avery <sup>7</sup>	+	-	+	7	+	+	-	+
McCrae <sup>33</sup>	-	-	+	14	+	-	-	+
Ogilvie <sup>24</sup>	+	-	+	7	+	+	-	+
Okuda <sup>34</sup>	-	-	+	7	+	+	-	+
Omichi <sup>37</sup>	+	-	+	0	-	+	-	+
Papandreou <sup>26</sup>	+	-	+	7	+	+	-	+
Parise <sup>25</sup>	+	-	+	7	+	+	-	+
Patel <sup>14</sup>	+	-	+	7	+	+	-	+
Sasaki <sup>27</sup>	+	-	+	0	-	+	-	+
Silva <sup>35</sup>	-	-	+	7	+	+	-	+
Wallace <sup>17</sup>	-	-	+	7	+	+	-	+
Westerberg <sup>36</sup>	-	-	+	14	+	+	-	+
Windred <sup>18</sup>	+	-	+	7	+	+	-	+

**Notes:** A priori aim/hypothesis: + indicates specific aims/hypotheses related to sleep regularity; - indicates no aim/hypothesis specific to sleep regularity. Sample size justification: - indicates unjustified. Sample representativeness: + indicates good representative sample; - indicates poor representativeness. Quality of sleep measures: + indicates well validated; - indicates not well validated. Quality of correlates measures: + indicates well validated; - indicates not well validated. Rates of missing in daily data: - indicates not reported. Inferences and conclusions: + indicates well-grounded inferences and conclusions. Figure Caption.

diseases.<sup>7,21,22,25</sup> Only one study examined health of the cardiovascular system directly and found high sleep duration variability was associated with high coronary artery calcium burden and abnormal ankle-brachial index.<sup>15</sup>

Almost all studies in this domain assessed sleep regularity objectively across only 3–7 days in large samples (N>1000). Results from this group were largely consistent in showing a negative correlation between sleep irregularity and cardiovascular health. Only one study assessed subjective sleep regularity with a sleep questionnaire, and this study reported non-significant association between self-reported variability in sleep duration and obesity.<sup>27</sup>

## Sleep Regularity and Cognitive Impairment/Dementia

Studies in this domain were highly heterogeneous in both sleep assessment methods and samples recruited. Sleep regularity was assessed using research-grade actigraphy, commercial smart watch, infrared motion sensor, and sleep diary. Intra-individual standard deviations of sleep duration, bedtime, onset latency, and fragmentation were all examined. Most studies included small samples of healthy older adults, MCI patients, and patients with dementia. Some studies included both patients and healthy older adults.

Four studies examined the relationship between sleep (ir)regularity and risk/biomarkers of dementia. Low sleep regularity was related to high risk of developing MCI or dementia, increased  $\beta$ -amyloid burden, and lower cortical thickness and gray matter volume.<sup>28–30,35</sup> However, results seem to differ between healthy older adults and MCI patients, and between the various measures of sleep (ir)regularity. One study reported high sleep duration variability was associated with increased  $\beta$ -amyloid burden in MCI patients,<sup>30</sup> while another study found high sleep fragmentation variability related to frontal amyloid burden in healthy older adults but not in patients with MCI.<sup>28</sup>

Four studies examined the relationship between sleep regularity and cognitive functions. Three found a significant negative relationship between sleep irregularity and cognitive performance<sup>30,34,36</sup> while the other one reported null results.<sup>33</sup> Such inconsistency may be related to methods of sleep assessments. The only study that reported non-significant relationship between sleep duration variability used a subjective sleep diary to track sleep.<sup>33</sup>

Two studies compared sleep (ir)regularity in persons belonging to different categories of cognitive function (healthy vs MCI vs dementia) and reported conflicting results. One study<sup>31</sup> found that patients with Alzheimer's disease had the lowest sleep regularity compared to MCI patients and healthy controls. When comparing MCI and health controls, however, this study found no significant difference. Another study also compared sleep regularity between MCI patients and healthy controls, but results showed that MCI patients had higher sleep regularity than healthy controls.<sup>32</sup> More studies comparing sleep regularity between the preclinical stages of dementia (MCI and healthy aging) are needed, to clarify the relationship between sleep (ir)regularity and the trajectory of cognitive decline towards MCI and Alzheimer's disease.

## Sleep Regularity and All-Cause Mortality

All three studies with large samples found that low sleep regularity was associated with premature mortality. Objectively assessed low sleep regularity was associated with increased mortality risk<sup>17</sup> and was found to be a stronger predictor of increased all-cause mortality risk than sleep duration.<sup>18</sup> Self-report irregular sleep pattern was also associated with increased all-cause mortality risk.<sup>37</sup>

## Discussion

### Summary of Findings

The current review is the first to examine health correlates of sleep regularity in older adults. The resultant literature, although limited in number, highlights the emerging importance of assessing sleep regularity on multiple health outcomes. All studies were published after 2010, and most had clear hypotheses about sleep regularity and health outcomes. High sleep regularity was consistently associated with lower risks of cardiovascular disease and all-cause mortality and to a lesser extent cognitive impairment/dementia risk.

Measures of body weight, such as obesity and BMI, were the most examined cardiovascular risk factors concerning sleep regularity (7 studies). In contrast, three studies examined hypertension status, two examined incidents of cardiovascular disease, and only one examined direct cardiovascular health index such as ankle-brachial index. The imbalance in outcome measures could be attributed to study designs. Most studies in this group used data collected by large-scale epidemiological research, where body weight measures were more common than measures of other cardiovascular risk factors. More studies with broader outcomes are needed to expand our understanding of how sleep regularity influences cardiovascular health in older adults.

Studies that examined cognitive impairments and dementia, on the other hand, mostly collected data instead of using existing epidemiological datasets. As a result, studies in this group had small sample sizes of less than 200. Devices used to track sleep also varied in this group, including research-grade actigraphy, self-report sleep diary, commercial smart-watch (Fitbit), and infrared motion sensor. It is possible that small sample sizes and different sleep assessment devices contributed to inconsistent results from this group. Large-scale studies with well-validated devices are needed for this topic.

Three recent studies with large sample sizes ( $N > 5000$ ) linked mortality with sleep regularity in older adults. The mean follow-up time from sleep assessment ranges from 7.8 years to 15 years. Sleep assessments from all three studies were collected at a single time point and for a short time period (eg 7 days). Longitudinal studies with multiple sleep assessments would provide more insight into how changes in sleep-wake patterns influence premature mortality risk. In particular, analysis of missingness data might yield additional insights about sleep behavior and its relation to health risk.

## Gaps and Future Directions

The most common assessment of sleep regularity was the intra-individual standard deviations. While standard deviation provides a straightforward and replicable assessment of regularity,<sup>38</sup> it is prone to systematic time effects (eg weekday weekend difference) that may inflate irregularity.<sup>39</sup> Furthermore, most studies used standard deviations with 7 days or less of sleep recordings to quantify sleep regularity. Mathematical models have shown significant fluctuations in standard deviations aggregated for 3 to 14 days.<sup>40</sup> Standard deviations calculated from short (less than 14 days) recording periods, therefore, may not be representative of one's sleep regularity. It is recommended that future studies record sleep for more than 14 days to better quantify regularity using standard deviations.<sup>41</sup>

Most studies, especially those in the cardiovascular health and mortality groups, used data collected by large-scale epidemiological research (eg MESA and UK Biobank). Although the advantages of using data from these research projects include large sample sizes and comprehensive health assessment, sleep was not the main outcome of these studies. As a result, these studies all had short actigraphy recording time and high missing data rate, such that some studies included subjects with only 2 or 3 nights of data. Results from these studies could be confounded by unstable standard deviations calculated from low quality, short recordings. Replication of the existing results with long and high quality actigraphy recordings is necessary.

Furthermore, comparison of results between studies was difficult due to the non-standardized assessment of sleep regularity across studies. Although most studies used standard deviations of sleep duration and bedtime, standard deviations of sleep fragmentation, efficiency, and onset latency were also examined by some studies. Additionally, the SRI<sup>10</sup> was examined by a few studies as well. The variety of sleep regularity metrics may provide some insights into the multidimensional aspect of sleep health. However, it would be useful to standardize the assessment of sleep regularity to enable comparison across studies and replication of results.

Another obstacle to comparing results between studies was the various devices used to assess sleep regularity. While most studies used wrist-worn actigraphy to track sleep, a few studies used other devices such as an infrared sensor and subjective questionnaires. Past studies have demonstrated that there are only weak correlations between subjective and objective sleep measures,<sup>42,43</sup> therefore results using different devices are not directly comparable. The heterogeneity observed in the group of studies examining the relationship between sleep regularity and cognitive functioning/dementia status may be attributed to the heterogeneous devices and methods used. Assessment of sleep regularity may be more suitable by objective devices than subjective recalls, especially in older adults whose memory is in decline.

Although low sleep regularity has been associated with negative health outcomes in older adults, the age-related difference in objective sleep regularity has not been clearly defined. Questionnaire-based studies found that older adults reported more regular sleep patterns than younger adults.<sup>6,44</sup> To our knowledge, there is no study comparing objective sleep regularity between older and younger adults. There is also a need for longitudinal studies to track changes in sleep regularity patterns. If old age is indeed associated with high sleep regularity, a decline in regularity could be used as a potent behavior risk marker predicting cardiovascular events and cognitive impairment/dementia by clinicians and researchers.

While discussing potential mechanisms for specific correlations is outside of the scope of this review, it is important to note that environmental factors such as sleep environment and culture also affect sleep regularity. Recent publications examining sleep patterns in users of commercial trackers across the globe showed that people in Asian countries had lower sleep regularity compared to people in Europe/North America.<sup>45</sup> Only 3 studies in the current review were conducted outside of Europe/North America, signaling a need for diversity and global collaboration in examining the health correlates of sleep regularity.

## Conclusion

In summary, the current review found that low sleep regularity was associated with worse cardiovascular health, increased risk of dementia and higher incidence of all-cause mortality in the aging population. Overall, the literature is small, but growing rapidly. Assessment of sleep regularity is not standardized and mostly inadequate. With the increasing popularity and accessibility of commercial wearable devices, future studies of aging on health should assess

sleep regularity as an important determinant. It is also important to standardize sleep regularity assessment methods. Lastly, sleep (ir)regularity likely has a bi-directional relationship with cardiovascular disease and cognitive impairment in older adults. Results from the current reviews are associational. Future interventional studies should explore the potential causal effects of sleep disorders, cardiovascular disease, and cognitive impairment.

## Disclosure

The authors report no conflicts of interest in this work.

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