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Authors

Fung, Constance H
Vitiello, Michael V
Alessi, Cathy A
et al.

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Report and Research Agenda of the American Geriatrics Society and National Institute on Aging Bedside-to-Bench Conference on Sleep, Circadian Rhythms, and Aging: New Avenues for Improving Brain Health, Physical Health, and Functioning

Constance H. Fung, MD, MSHS[*,†], **Michael V. Vitiello, PhD**[‡], **Cathy A. Alessi, MD**[*,†], **George A. Kuchel, MD**[§], and **the AGS/NIA Sleep Conference Planning Committee and Faculty**[1]

[*]Geriatric Research, Education and Clinical Center, Veterans Affairs Greater Los Angeles Healthcare System

[†]David Geffen School of Medicine, University of California, Los Angeles, Los Angeles, California

[‡]Psychiatry and Behavioral Sciences, University of Washington, Seattle, Washington

[§]Center on Aging, University of Connecticut Health Center, Farmington, Connecticut

Abstract

The American Geriatrics Society, with support from the National Institute on Aging and other funders, held its eighth Bedside-to-Bench research conference, entitled “Sleep, Circadian Rhythms, and Aging: New Avenues for Improving Brain Health, Physical Health and Functioning,” October 4 to 6, 2015, in Bethesda, Maryland. Part of a conference series addressing three common geriatric syndromes—delirium, sleep and circadian rhythm (SCR) disturbance, and voiding dysfunction—the series highlighted relationships and pertinent clinical and pathophysiological commonalities between these three geriatric syndromes. The conference provided a forum for discussing current sleep, circadian rhythm, and aging research; identifying gaps in knowledge; and developing a research agenda to inform future investigative efforts. The conference also promoted networking among developing researchers, leaders in the field of SCR and aging, and National Institutes of Health program personnel.

Keywords

aging; circadian; disorders; interventions; sleep

Sleep and circadian rhythms (SCRs), which are fundamental biological imperatives, may change with advanced age, but in addition, are often challenged by environmental changes, unhealthy behaviors, and disease, leading to SCR disturbances and, ultimately, adverse health outcomes. Older adults often describe difficulty maintaining sleep, excessive daytime sleepiness, and daytime napping; SCR disturbances increase in prevalence with advanced

Address correspondence to Anna Mikhailovich, American Geriatrics Society, Special Projects, 40 Fulton Street 18th Floor, New York, NY 10038. AMikhailovich@americangeriatrics.org.

[1]AGS/NIA Sleep Conference Planning Committee and Faculty members are listed in Appendix. Public Policy, American Geriatrics Society, New York, New York.

age, and many health conditions that are common in older adults are also associated with disturbed sleep. Recent advances in the scientific knowledge regarding sleep and circadian biology in animal models and humans indicate that SCR disturbances can play a central role in the expression and development of disease,[1] including disturbances culminating from habitual exposure for many decades to artificial light at night and shiftwork.[2] Chronic SCR disturbances result in sleep deficiency, which has been linked to greater risk of a wide variety of illnesses, including depression; cancer; and cardiovascular, metabolic, and neurodegenerative disorders. Sleep insufficiency has also been associated with cognitive and motor performance deficits and greater risk of accidents, including falls.[3,4]

Examining the relationship between SCRs and health is particularly relevant to research involving older adults, because the prevalence of SCR disturbances and certain health problems (e.g., cardiometabolic and neurodegenerative disorders) increase with age.[5–7] SCR-based preventive and disease-specific strategies could yield transformative approaches to maximizing healthy aging. Clarifying the relationships between SCR biomarkers, health states, and the aging process, for example, may provide insight into novel ways to detect, monitor, and treat common diseases that occur more frequently in older than younger adults.[8,9] Given the broad effects of SCRs on brain and physical health and functioning (Figure 1) and the complex health conditions that arise with aging, research efforts that employ interdisciplinary and multidisciplinary approaches may yield the most-promising strategies.[10]

SCR CONCEPTUALIZED AS A POSSIBLE GERIATRIC SYNDROME

Geriatric syndromes are characterized by a set of health conditions that co-occur, typically producing a single phenomenology (pattern of symptoms and signs) and rendering older adults vulnerable to situational challenges.[11,12] The concept of the geriatric syndrome has shaped geriatric research, clinical practice, and policy for longer than 2 decades. Well-described geriatric syndromes include delirium, which was the focus of the seventh American Geriatrics Society (AGS), National Institute on Aging (NIA) Bedside-to-Bench conference (National Institutes of Health Research Conference Cooperative Agreement Program (U13)), and incontinence, which will be the focus of the next conference in this series. Geriatric syndromes such as delirium and incontinence have been conceptualized as sharing a set of risk factors (e.g., older age, cognitive impairment, functional impairment, impaired mobility) that contribute to frailty, which in turn feeds back on the shared risk factors and the geriatric syndromes. Frailty leads to poor outcomes such as disability dependence, nursing home placement, and death.[12] Geriatric syndromes may be contrasted with traditional medical syndromes, which are typically characterized by multiple phenomenologies (patterns of symptoms and signs) resulting from a single underlying etiological or morbid process.[13]

Although delirium and incontinence have long been included in the list of geriatric syndromes, consideration of SCR disturbance is newer. SCR disturbance in older adults is similar to other health states classified as geriatric syndromes and therefore may fit into the conceptual model described above. Risk factors similar to those that delirium and incontinence share—older age, cognitive impairment, functional impairment, and impaired

mobility—influence SCR disturbance.[14–18] SCR disturbance is also associated with greater risk of frailty,[19] which in turn may worsen SCR disturbance, and frailty itself is also associated with poor outcomes. By recognizing and approaching SCR disturbance as a geriatric syndrome, researchers may be able to leverage and apply translational research methods that have been used to study other geriatric syndromes such as delirium and falls and adapt strategies to shape clinical practice and policy. Approaching SCR disturbance as a geriatric syndrome may also accelerate improvements in the care of older adults with these conditions.

SCR AND HEALTH IN AGING

At the conference, faculty provided short overviews of the effect of SCR disturbance on health in the context of aging within four broad domains: brain health, physical health, functional status and quality of life, and habitual sleep duration and health. Overviews addressed important areas of research in each of these domains rather than a comprehensive description of all relevant research on SCR and aging. Summaries of these overviews for each domain follow.

SCRs and Brain Health in Aging

SCR and Neurodegeneration—In modern society, short sleep duration is pervasive, and it is commonly assumed that the effects of sleep loss on the brain are readily reversible with weekend recovery sleep. This assumption has never been confirmed in human studies. Rather, some research suggests that impaired vigilance that occurs after 1 week of short sleep is not fully reversed even after three nights of recovery sleep.[20,21] Thus, the consequences of repeated chronic short sleep duration on the brain as reported in experimental studies that model the typical modern work week are largely unexplored. In adult mice, repeated days of short sleep duration interspersed with long recovery sleep “weekends” result in lasting behavioral, neuroanatomical, and molecular abnormalities.[22] Specifically, short sleep for three consecutive days results in loss of locus coeruleus neurons and oxidative stress in surviving neurons. Similar consequences are observed with sleep fragmentation (repetitive short interruptions of sleep) despite normal sleep times overall, again involving oxidative stress, breakdown of mitochondrial homeostasis, and loss of locus coeruleus neurons.[23] Loss of locus coeruleus neurons has been shown to advance cognitive decline in animal models of Alzheimer’s disease and neurodegeneration in a model of Down syndrome, whereas supplementing animals with a noradrenergic precursor improved cognition in an animal model of Alzheimer’s disease.[24–26] Thus, chronic sleep loss and sleep disturbance may have lasting significant effects on brain health. Moreover, current research collectively supports the concept that chronic sleep loss may speed the onset of certain symptoms of aging and age-related neurodegenerative processes, particularly involving neurons that are activated with arousal and, in turn, modulate wakefulness (wake-activated neurons).

SCR and the Glymphatic System—Another aspect of brain health that sleep affects is neuronal waste product removal. The brain is a highly metabolically active organ, and removal of excess fluids and waste products of neurons is critical for normal brain function.

The brain parenchyma has no authentic lymphatic vessels for detoxification. Recent research suggests that a macroscopic waste clearance system in the brain (glymphatic system), which involves a network of perivascular tunnels that astroglial endfeet form on the outside where aquaporin 4 water channels are highly expressed, allows cerebrospinal fluid to circulate and interchanges with interstitial fluid, thereby allowing elimination of soluble proteins and metabolites (such as β-amyloid) from the central nervous system.[27,28] Research suggests that the activities of the glymphatic system take place mainly during sleep, suggesting that at least one aspect of the biological need for sleep may be attributed to the necessary elimination of potentially toxic waste products in the brain. In addition, impairment of glymphatic function may be involved in certain neurodegenerative disorders and other brain conditions associated with advanced age.[29,30] Because of its perivascular location, the glymphatic system relies on brain vasculature to function, but it is unclear how perivascular neurons, gliovascular interactions, and vascular processes change and interfere with glymphatic pathway functioning in normal aging and disease.

SCR and Central Nervous System Inflammation—The relationship between sleep and central nervous system inflammation is another important aspect of brain health and aging. Neuroinflammation, including activation of microglia and increases in proinflammatory cytokine levels in the brain, has been associated with cognitive decline. Likewise, insufficient sleep has been associated with neuroinflammation, and sleep disturbance and neuroinflammation are well-defined changes with age,[31,32] suggesting a possible mechanism of sleep effects on brain health and disease. Older brains are generally inflamed,[33] and research suggests that sleep disturbance alters gene expression and proteins of inflammatory mediators.[34,35] The role of nonneuronal cell types in brain responses to sleep loss is increasingly acknowledged, and glial cells (including microglia and astrocytes) may play a role in the relationship between sleep and neuroinflammation with aging.[36] Effects of aging and disease on neuroinflammation may also involve the hypothalamic suprachiasmatic nucleus, which is the pacemaker of circadian rhythms that regulates sleep–wake and other physiological processes.

SCR, Cognitive Function, and Neurodegenerative Disorders—Recent studies support a relationship between age-related changes in SCRs and simultaneous changes in cognition. In addition to having less-robust circadian rhythms,[37] older adults can have a shift in chronotype (the propensity to be asleep or awake at a particular time over 24 hours); whereas younger adults are more likely to be evening types (owls),[38] older adults are more likely to be morning types (larks).[39] This shift in chronotype with age reflects a shift in the time of peak alertness and optimal performance on cognitive assessments,[40,41] and it has been suggested that age-related impairments are less severe when older adults are tested at their preferred time with respect to their chronotype.[42] Age-related changes in sleep quantity and architecture may also underlie cognitive decline.[4] Sleep contributes to the consolidation (stabilization) of memories. In young adults, memories are consolidated over an interval of sleep, resulting in memories that are more stable and more efficiently retrieved.[43] Sleep enhances procedural memory (long-term memory of how to perform different actions and skills, a type of nondeclarative memory), and changes in sleep impair procedural memory consolidation in older adults. Declarative memory (memory of facts and events, which is

thought to depend on the hippocampus and medial temporal lobe) may also be consolidated with sufficient sleep time.[44]

In addition to these age-related changes in sleep associated with brain health, SCR disturbances are common in neurodegenerative diseases and may contribute to disease pathogenesis. Much of this evidence is focused on SCR abnormalities in Alzheimer's disease.[45–47] The potential mechanisms by which SCR disturbances might be involved in the pathogenesis of Alzheimer's disease and other neurodegenerative conditions have focused on the regulation of β-amyloid,[48] inflammation, and oxidative stress through the sleep–wake cycle and the circadian clock.[49] Potential therapeutic targets involving the sleep–wake cycle and the circadian clock are being studied as opportunities to combat neurodegeneration.

The most common sleep disorder, insomnia, is associated with depression,[50,51] impaired cognitive function,[4,52] dementia,[53] and delirium.[54] Several plausible biological mechanisms may underlie these associations. For instance, disturbances in sleep and circadian function, including those seen with insomnia, may contribute to altered function of neural circuits, sympathetic–parasympathetic imbalance, altered immune function, systemic inflammation,[55] and poor glymphatic clearance of β-amyloid (as described above).[30,56] Treatment of insomnia in older adults includes pharmacological and behavioral approaches. Pharmacological treatments are efficacious[57] but in older adults are associated with a number of potentially serious adverse effects, including excessive sedation, falls, hip fracture,[58] and possibly greater risk of dementia[59] and death.[60] Behavioral treatments are also efficacious[57,61] and improve not only sleep and daytime symptoms of insomnia, but also possibly some of the dysregulated mechanisms noted above.[62,63] Effective behavioral treatments for insomnia (as opposed to the routinely prescribed but typically ineffective "sleep hygiene" advice) need to be further disseminated for maximal effect.

SCR and Physical Health in Aging

In addition to evidence of the associations with brain health described above, there are relationships between SCR disturbance, aging, and physical health.

SCR and Metabolism—Age-related SCR disturbances have implications for metabolic dysfunction,[7,64,65] including obesity and diabetes mellitus (especially in adults aged ≥65[66]) and the physiological and medical burden of these conditions.[5,66–69] Findings from studies examining age-related changes in SCR disturbance in rodent models have demonstrated their effect on health and metabolism.[70–73] Changes in central and peripheral clocks contribute to age-related changes in metabolic health, which may vary according to organ system and may be reversible. These changes are potential targets for intervention. Age-related changes in SCRs may contribute to and interact with changes in nutrient intake, energy expenditure and resting metabolic rate, physical activity (exercise, nonexercise, sedentary time), and ultimately sarcopenia. Increases in the number of older people working and shiftwork may also contribute to the incidence of metabolic disease.[74] Sex differences in age-related SCR disturbance and age-related changes in sex hormones may contribute to metabolic disease, and it is likely that there are bidirectional relationships between metabolic disease and SCR disturbance in older adults.[75]

SCR and Cardiovascular Health—Evidence suggests that SCR disturbances also affect another important aspect of physical health: blood pressure (BP). High BP, the largest contributing risk factor to cardiovascular disease (CVD) mortality, increases with age, and more than 90% of CVD events occur in people aged 60 and older.[76] In the United States, nearly two-thirds of individuals aged 60 and older have high systolic or diastolic BP based on daytime office BP measurements.[77] Nonetheless, the U.S. Preventive Services Task Force[77] and other authorities[76] report that daytime office BP measurement is of poorer diagnostic accuracy and prognostic value for future CVD events than around-the-clock ambulatory BP monitoring, resulting in the recommendation that around-the-clock ambulatory BP monitory, rather than office BP measurements, be the reference standard for the diagnosis of high BP. Mean asleep systolic blood pressure derived using around-the-clock ambulatory BP monitoring is more strongly correlated with development of end-organ (vascular, renal, cardiac) injury, type 2 diabetes mellitus, and future CVD events than awake mean systolic BP derived from around-the-clock ambulatory BP or daytime office BP measurements, and the incidence of high asleep systolic BP increases steadily after 45 years of age. Bedtime chronotherapy of conventional antihypertensive medications (timing of the medications relative to circadian rhythm determinants of hypertension to optimize the beneficial effects and tolerance of the medications) improves asleep systolic BP and reduces CVD risk and events substantially more than morning scheduled dosing.[78]

There is also evidence of and association between sleep-disordered breathing (SDB) and cardiovascular health. SDB increases in prevalence with aging[79] and, in older adults, is associated with CVD[80,81] and death,[81,82] as well as other adverse outcomes such as cognitive dysfunction,[83] but limitations in the definitions and diagnostic criteria for SDB have made it difficult to understand how to best define and measure it in older adults. A topic of considerable debate is whether treatment of mild SDB confers benefit. Chronic intermittent hypoxia (from mild SDB) may be cardio- and neuroprotective, particularly in older people.[83,84] There are also limitations to the understanding of when and how to treat central sleep apnea, which also increases in prevalence with age.

SCR and Pain—Another aspect of physical health that is associated with SCR disturbance is pain. Sleep disturbances and chronic pain are two highly prevalent comorbidities associated with aging, and research indicates that these often under-treated comorbidities may reciprocally interact.[85] Findings of experimental studies show that sleep disturbance and sleep loss may alter quantitative sensory measures of pain in humans. Sleep loss may amplify pain, and preliminary data suggest that treating sleep problems may improve chronic pain management. Multiple controlled experiments have demonstrated that various forms of partial and total sleep loss induce hypersensitivity to noxious painful stimuli and promote failure of endogenous descending pain modulation.[85] Longitudinal data strongly indicate that complaints of poor sleep predict development of chronic pain and pain exacerbation, perhaps more robustly than pain predicts future sleep disturbance.[85] The mechanisms of sleep disturbance–induced hyperalgesia are poorly understood, but inflammation and impaired descending pain inhibition are promising candidate mediators.[86,87] The translation of these findings from research to clinical use (through randomized clinical trials) testing whether treating insomnia improves pain outcomes is just

beginning to be undertaken, with some especially promising preliminary results in older adults with osteoarthritis.[88–90]

SCR and Nocturia—Nocturia is an extremely common cause of poor sleep in older age.[91] It has typically been viewed as a urological problem and of relatively little consequence, unless its presence "bothers" the individual. How "bother" is defined and what constitutes nocturia have been subjects of great debate. Nocturia compromises quality of life and may portend adverse outcomes, such as sleep fragmentation and loss, with greater risk of depressed mood, falls, and hip fractures. Nocturia results from multiple causes, but sleep apnea is an overlooked cause in men and women, whereas prostatic hyperplasia is vastly overrated as a cause of nocturia in older men. Age-dependent increases in nocturnal urine production, reflecting relative underproduction of arginine vasopressin at night in old age, may be associated with nocturia and represent an otherwise normative change in the circadian timing system in women and men. A particularly intriguing question is whether urinary urgency triggers awakenings or whether disrupted sleep from other causes leads to nocturnal voiding episodes by increasing awareness of bladder fullness.[92] Interventions such as positive airway pressure therapy (when sleep apnea is involved), sedative–hypnotics, behavioral interventions[93] targeting fluid intake and bladder control exercises, medications for overactive bladder, and hormone replacement (e.g., arginine vasopressin analogues) may all have a role in treating nocturia.

SCR and Falls—Falls occur in approximately one-third of older adults each year, leading to greater risk of functional impairment, fracture, and mortality. Some evidence suggests that poor sleep may predispose older adults to greater risk of falls,[3,94] and the medications used to treat sleep problems (in particular sedative–hypnotics) also increase risk of falls.[95,96] The independent effects of poor sleep and sleep medications on fall risk are not clearly established. Self-reported assessment of sleep has limited previous studies. Furthermore, the relationship between sleep, hypnotic use, and risk of fractures and other injuries resulting from falls is not well understood. In addition, because causes of falls are multi-factorial, other conditions related to fall risk and sleep problems (e.g., urinary incontinence) should also be taken into account. Given the current observational evidence linking sleep, hypnotic use, and risk of falls and fractures, there is a need for randomized comparative effectiveness studies to determine which treatments (considering pharmacological and behavioral) for sleep problems offer the best balance between better sleep and safety for older adults. Other factors such as urinary incontinence, frailty, comorbidities, and health status are likely to be important mediators to consider in the relationship between sleep and falls.

SCRs, Functional Status, and Quality of Life in Older Adults and Special Populations

Increasing evidence suggests important consequences of SCR disturbance on the functional status and quality of life of older adults. For example, self-reported daytime sleepiness has been demonstrated to have a moderate to large adverse association with several domains of function, including social outcomes, general productivity, vigilance, activity level, and global functional status.[97] Evidence of a relationship between nighttime sleep and self-reported measures of functional status (basic and instrumental activities of daily living) has been mixed,[98,99] although there is convincing evidence of an association between poor

nighttime sleep; impairment in measures of physical function, such as weaker grip strength and slower walking speed; and self-reported level of physical activity.[100] The relationship between sleep and quality of life in older adults has been well demonstrated. For example, insomnia identified using simple questions[101] or based on clinical interview[102] is associated with worse quality of life in older adults. Short (≤6 hours per night) and long (≥9 hours per night) sleep duration have been associated with poor quality of life in older adults.[103] The relationship between sleep complaints and worse quality of life is even more notable in older adults with greater comorbidity.[104]

Daytime Sleepiness and Napping—When considering SCRs, functional status, and quality of life in older adults, it is important to consider daytime sleepiness and napping. Daytime sleepiness and napping have been measured in a variety of ways and have been studied as important metrics of daytime functioning in older adults.[105] Both are related to many aspects of health and nighttime sleep[106,107] Daytime sleepiness can be assessed through self-report or objectively using sleep latency testing. Napping has been assessed through self-report, but there has been great variation in questions used to ask about napping. Total 24-hour sleep patterns can also be assessed using actigraphy combined with a sleep diary. Regardless of the methods of assessment, daytime sleepiness and napping are associated with poor underlying health status and are strong independent predictors of mortality.[107] Related interventions have targeted underlying health conditions, compromised nighttime sleep, and inadequate physical activity. It is not clear whether napping should be recommended to older adults, but studies have shown it can have short-term benefits for daytime functioning.

SCR in the Acute-Care Hospital and Institutional Settings—Older adults make up a large portion of hospitalized and institutionalized individuals, which suggests that it is important to understand how the well-recognized acute sleep loss of hospitalization affects inpatients, particularly those that are older and at risk of the hazards of hospitalization and the recently described “posthospital syndrome,”[108] and to understand SCR disturbance in institutionalized individuals. Given the prevalence of undiagnosed sleep disorders (e.g., sleep apnea) in chronically ill individuals, the question arises as to whether hospitalization constitutes an opportune time to screen and treat undiagnosed sleep disorders that may also affect health outcomes.[109,110] Noise, light, and other aspects of the acute hospital environment appear to contribute to sleep disturbances in this setting.[111,112] Sleep loss in the acute inpatient setting may also be associated with important outcomes.[113] SCR disturbance is common in institutionalized older adults and is typically associated with multiple causes and comorbidities. Various sleep-promoting interventions, such as bright-light therapy,[114] melatonin,[115] and exercise,[116,117] have been studied in this population. Recent evidence suggests a relationship between restless legs syndrome and sundowning,[118] and a newly developed restless legs syndrome diagnostic measure suitable for institutionalized older adults with cognitive impairment has been proposed.[119]

Habitual Sleep Duration and Health in Aging

There has been considerable interest and controversy in recent years about the potential association between habitual sleep duration and important health outcomes. The prevailing

perspective is that short and long sleep duration patterns are independent predictors of all-cause mortality,[120–123] but interpretation of the existing literature is difficult given potential confounding by SDB and the common reliance in study methods on a single time point to represent habitual sleep duration. The Sleep Heart Health Study (SHHS) found that adjusted hazard ratios (HRs) of death were 0.98 (95% confidence interval (CI) = 0.87–1.10) for short sleep duration and 1.25 (95% CI = 1.05–1.47) for long sleep duration (reference normal sleep duration). After accounting for covariates and potential confounders, there was 79% higher mortality in SHHS participants who transitioned from short to long habitual sleep duration (HR = 1.79, 95% CI=1.13–2.85) and a 61% increase in mortality in subjects who transitioned from normal to long sleep duration (HR = 1.61, 95% CI = 1.23–2.10).

Nonetheless, some experts argue that the causality of the association between long sleep duration and mortality has not been definitively established. Many[122,124–129] but not all[130–133] cohort studies of sleep and mortality in older adults have identified an association between long sleep duration and mortality after adjustment for known and measured confounders. Although the association is noted even after excluding individuals with known comorbidity, there is notable variation in the characterization of the populations and potential confounders. Furthermore, objective sleep assessment is typically lacking in these studies. Confounders, such as obesity, mood disorders, sedentary lifestyle, living alone, alcohol use, lower income or education, and cognitive impairment,[68,128,131,134–138] as well as SDB and depression,[133,134,139–141] that are associated with sleep duration, and not intrinsically long sleep itself, may account for the association between sleep duration and mortality and morbidity. Objective assessments of sleep duration and further characterization of confounders including SDB (home sleep testing); adiposity; inflammation; sedentary lifestyle (accelerometry[142]); and measurements of mood, functional ability, sedative–hypnotic use, and socioeconomic factors and access to care are needed to better define the relationship between long sleep and mortality.

FUTURE RESEARCH PRIORITIES

Before the conference, registrants submitted important questions regarding their perceptions of gaps in the area of SCR and aging research. Synthesis of this initial input and discussions at the conference resulted in identification of a number of research priorities. The identified areas of research priority were relationship between SCR and aging; relationship between SCR, health conditions and functional status, and health services in individuals, their caregivers, and their bedpartners; treatment of SCR disturbances and implementation of treatments; disparities in SCRs, other clinical outcomes, functional status, quality of life, and health services; and SCR research workforce. These areas were further specified with more-detailed recommendations for research priorities (Table 1).

Improvement in measurement of SCRs and SCR disturbances was also identified as essential so as to better understand the relationships between SCRs, aging, and important health outcomes. For example, measuring SCRs in nonclinical environments such as in individuals' homes using clinical grade nonintrusive wearable sensor technology that enables around-the-clock data gathering may help advance understanding of these relationships; identifying methods to mine SCR data from large databases (e.g., electronic health records) may also be

useful. Adding SCR measures to ongoing and future cohort studies may also be an efficient method of obtaining important SCR data. Coordinated efforts, such as through development of a universal toolbox of SCR measures, could also facilitate the development and use of large databases.

CONCLUSIONS

SCR research has tremendous potential to improve brain and mental health, physical health, and functioning in older adults. SCR-based strategies hold the promise of altering the development and expression of diseases that are common in older adults and of improving their functional status and quality of life. Insightful research on SCR disturbance is needed to realize this potential. The recent Bedside-to-Bench research conference on SCR and aging fostered an exchange of SCR-aging research ideas and mentoring among current and developing researchers in the interface of SCR and aging research. It provided a unique opportunity for leading researchers in the field along with the next generation of SCR-aging researchers to develop a research agenda collaboratively, which it is hoped will help drive future productive research efforts in this area. It also provided a forum for the development of new research collaborations to address the important areas of SCR research detailed in the workshop's agenda. Continuing efforts to ensure execution of this research agenda and ultimately improve the health of older adults are needed, including implementing policies to cultivate new investigators and to support ongoing research on SCR and aging.

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APPENDIX

Multiple authors were engaged in the preparation of this paper through service on the Writing Group and the Planning Committee and as presenters. The following key identifies how an author was engaged with this paper: Writing Group (1), Planning Committee (2), Presenter (3). Alphabetical listing of authors: Cathy Alessi, MD, David Geffen School of Medicine, University of California, Los Angeles, CA and Veterans Affairs (VA) Greater Los Angeles Healthcare System, Los Angeles, CA (1,2,3); Vineet Arora, MD, MAPP, Pritzker School of Medicine, University of Chicago, Chicago, IL (3); R. Nisha Aurora, MD, School of Medicine, Johns Hopkins University, Baltimore, MD (3); Helene Benveniste, MD, PhD, School of Medicine, Stony Brook University, Stony Brook, NY (3); Donald Bliwise, PhD, School of Medicine, Emory University, Atlanta, GA (3); Daniel Buysse, MD, School of Medicine, University of Pittsburgh, Pittsburgh, PA (2, 3); Constance H. Fung, MD, MSHS, David Geffen School of Medicine, University of California, Los Angeles, CA and VA Greater Los Angeles Healthcare System, Los Angeles, CA (1,2); Michael R. Irwin, Cousins Center for Psychoneuroimmunology, Semel Institute for Neuroscience, David Geffen School of Medicine, University of California, Los Angeles, CA (3); George A. Kuchel, MD (Principal Investigator for the Series of Bedside-to-Bench Conferences), University of Connecticut Health Center, Farmington, CT (1,2); Erik Musiek, MD, PhD, School of Medicine, Washington University in St. Louis, St. Louis, MO (3); Anne B. Newman, MD, MPH, Graduate School of Public Health, University of Pittsburgh, Pittsburgh, PA (3); Daniel O'Hearn, MD, Oregon Health & Science University, Portland, OR (3); Mark R. Opp, PhD, School of Medicine, University of Washington, Seattle, WA (3); Barbara Phillips, MD, MSPH, College of Medicine, University of Kentucky, Lexington, KY (2, 3); Naresh Punjabi, MD, PhD, Johns Hopkins University, Baltimore, MD (3); Kathy Richards, PhD, RN, School of Nursing, College of Health and Human Services, George Mason University, Fairfax, Virginia (2, 3); Robert Schwartz, MD (Planning Committee Co-chair), Eastern Colorado Health Care System (Denver) VA Geriatric Research, Education, and Clinical Center, Denver, CO and School of Medicine, University of Colorado Anschutz Medical Campus,

Aurora, CO (2); Michael Smith, PhD, Johns Hopkins University, Baltimore, MD (3); Michael Smolensky, PhD, University of Texas at Austin, Austin, TX (3); Rebecca Spencer, PhD, University of Massachusetts, Amherst, Amherst, MA (3); Katie Stone, PhD, California Pacific Medical Center Research Institute, San Francisco, CA (3); Carlos Vaz Fragoso, MD, School of Medicine, Yale University, New Haven, CT (3); Sigrid Veasey, MD, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA (3); Michael V. Vitiello, PhD (Planning Committee Co-chair), University of Washington, Seattle, WA (1,2,3); Kenneth Wright Jr., PhD, University of Colorado Boulder, Boulder, CO (2, 3); Phyllis Zee, MD, PhD, Feinberg School of Medicine, Northwestern University, Chicago, IL (2, 3).

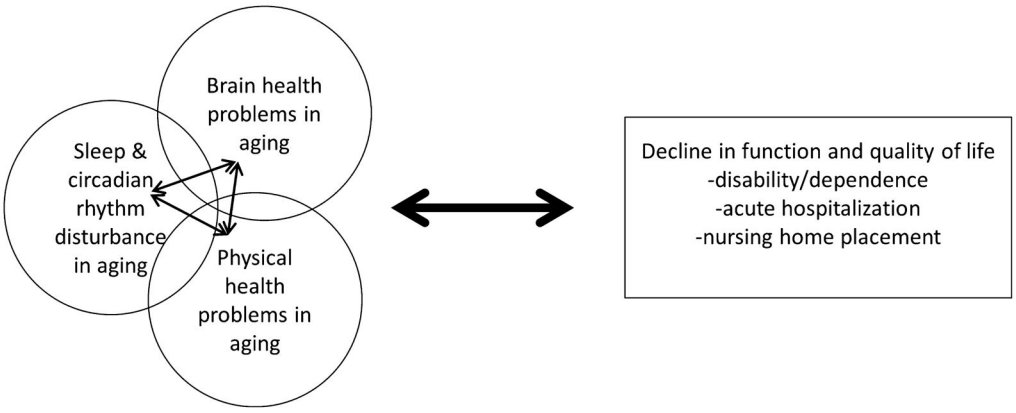

Figure 1.

Sleep and circadian rhythm disturbances, brain health problems, and physical health problems in aging may overlap and interact with one another. These problems are conceptualized to have a reciprocal relationship with daytime function and quality of life. Decline in function and quality of life may manifest clinically as greater disability and dependence, hospitalization, or nursing home placement.

Table 1

Research Agenda

Domain	Research Questions
Relationship between SCR and aging (including the underlying fundamental, basic mechanisms)	What changes in SCR occur in optimally aging adults? Does the "need" to sleep change with age?
Relationship between SCR, health conditions and function, and health services in individuals, their caregivers, and their bedpartners	SCR disturbances can be precipitators, consequences, or modifiers: Precipitator: How do SCR characteristics and disorders affect the following "outcomes": physiological changes that occur with aging, diseases and health conditions (especially falls, cognitive impairment), physical activity, functional status, quality of life, healthcare utilization, cost, and quality of care? Consequence: How do physiological changes that occur with optimal aging, disease, health conditions, physical activities, and functional impairment affect SCR characteristics and disorders? Modifier: To what extent do individual characteristics and location or population of study (e.g., "real world") modify the relationships above?
Treatment of SCR disturbances and disorders and implementation of treatments[a]	What are the best ways to manage sleep disturbance and disorders? What are best ways to manage circadian rhythm disturbance and disorders? How can we optimize sleep across various circadian rhythm disorders and for different chronotypes? How do treatment of SCR disturbance and treatments that modify sleep patterns and circadian rhythms affect other clinical outcomes, functional status, quality of life, healthcare utilization, cost, quality of care (quality of care of other health conditions and functional impairment)? What are the favorable and unfavorable effects of medication on sleep in older individuals in inpatient and outpatient settings? What are the interactions between medications and circadian rhythms, and how do these interactions affect the favorable and unfavorable effects of medications? What are the optimal methods of developing and implementing an individualized approach to SCR treatment, accounting for personal preferences and physiological differences in risk factor profiles among individuals? What are the optimal ways of implementing and testing SCR treatments in "real world" settings (nursing homes, hospitals, homes)?
Disparities in SCR, other clinical outcomes, functional, quality of life, and health services	What types of disparities (e.g., age, sex, race and ethnicity, socioeconomic status, geographic region, epigenetics) are present in the diagnosis and treatment of SCR disorders? How do these disparities affect SCR and other clinical outcomes, functional status, quality of life, quality of care, healthcare utilization, and healthcare costs? To what extent and through what mechanisms do SCR and SCR disorders contribute to health disparities and inequities in clinical, functional, quality-of-life, and health services outcomes?
The SCR research workforce and funding	What are the optimal funding mechanisms to advance research on SCR and aging? What infrastructure, programs, and funding are needed to cultivate and foster a trained, multidisciplinary workforce to address the questions outlined in this research agenda?

[a]Because many processes contribute to sleep and circadian rhythm (SCR) disturbance in older adults, treatments that are multicomponent and that target multiple risk factors may be necessary to improve SCR and other health outcomes in older adults.