NATIONAL INSTITUTES OF HEALTH

SLEEP RESEARCH PLAN

Advancing the Science of Sleep & Circadian Biology Research
Foreword

The National Center on Sleep Disorders Research (NCSDR), established under a provision of the National Institutes of Health (NIH) Revitalization Act of 1993, began its work with an ambitious mission: to conduct and support research and training related to sleep disorders, coordinate sleep and circadian activities across NIH and the federal government, and educate the research community and the public about this work. This 2021 NIH Sleep Research Plan showcases the vigorous efforts the NCSDR is making to honor that mandate.

Landmark scientific discoveries have shown how significant sleep and circadian biology is to human health and disease and how sleep deficiencies may differ across populations. As this research progresses, the evidence that sleep is a nonnegotiable biological requirement for overall mental and physical health and wellness is becoming even more clear. The growth of sleep and circadian research in traditional areas such as genetics and neuroscience, the emerging research on sleep health disparities, and the need to explore sleep health across the lifespan of women all underscore how much more there is to learn. The recognition and subsequent integration of sleep and circadian biology across NIH research domains remains an important goal.

In this 2021 NIH Sleep Research Plan, exciting opportunities have been identified to advance the research in these fields. It has done this through a transparent and iterative process, with input from the Sleep Disorders Research Advisory Board, the NIH Sleep Research Coordinating Committee, patient advocates, academic leaders, and healthcare providers. Key features of the plan focus on elucidating sleep and circadian mechanisms that underlie health and disease, accelerating implementation research, and understanding the role of sleep in health disparities.

The plan also promotes fostering a strong and diverse scientific workforce. This aim is reinforced by the recently launched NIH UNITE initiative, which was established to identify and address structural racism within the NIH-supported and the greater scientific community.

Progress in sleep and circadian research is a continually evolving process that involves consistent engagement and communication with key stakeholders in order to maximize advancements. The research activities presented in 2021 NIH Sleep Research Plan will not only enhance sleep and circadian biology research, but potentially transform medicine and public health. Implementation of the advancements made in these fields could greatly advance the public’s health and well-being, and this plan offers important strategies and ideas to achieve these goals.

Francis S. Collins, M.D., Ph.D.
Director
National Institutes of Health
NCSDR Director’s Message

It is with great pleasure that the National Center on Sleep Disorders Research (NCSDR), the National Heart, Lung, and Blood Institute (NHLBI), and the NIH Sleep Research Coordinating Committee (SRCC), present the 2021 NIH Sleep Research Plan. This plan builds on the growth of sleep and circadian biology research over the past decade and highlights critical research needs and opportunities for the coming years.

The process of updating the 2021 NIH Sleep Research Plan started with the release of a Request for Information (RFI) from the NIH. The RFI invited ideas for cutting edge sleep and circadian-related research that could have the highest impact on biomedical sciences and on public health. It also sought information about impediments that could slow or upend such advances. This plan represents thoughtful input from the public and scientific communities, guidance from the Sleep Disorders Research Advisory Board, coordination across the SRCC, and feedback from NIH leadership.

Sleep and circadian biology research holds much promise for the health, safety, and well-being of the nation. The 2017 Nobel Prize in Physiology or Medicine, which recognized the discovery of molecular mechanisms controlling circadian rhythms, ignited greater interest in the interactions between biological rhythms and drugs. In doing so, it offered hope that we could one day answer many intriguing and important questions, such as what time of day is best for administering therapies and interventions like vaccines, anti-hypertensives, and certain chemotherapies.

Harnessing this emerging knowledge could inspire other transformative discoveries — for example, biomarkers that accurately and objectively indicate sleep and circadian disorders or sleep deficiency. Such findings could lead to improvements in the lives of people with chronic conditions, such as heart disease, obesity, diabetes, depression, dementia, and certain cancers. Consider the possibilities: cost-effective, sleep and circadian-based interventions that have the potential to impact a wide range of suboptimal health outcomes that have been associated with sleep deficiency.

Fostering an appreciation of cultural differences that contribute to disparities in sleep health presents a path forward that may help eliminate health inequities. A more in-depth understanding of the mechanisms and causal pathways that account for sleep health disparities, as well as exploring the contributions of sex and/or gender influences on sleep, could ultimately inform public health policies.

It has been 28 years since federal legislation created the NCSDR to support research, disseminate health information, and coordinate sleep and circadian research activities across the NIH and the government. In collaboration with our federal partners and public stakeholders, NCSDR will continue to facilitate the research that addresses the needs and opportunities presented in the revised plan. As always, we will do this with our eyes on one prize: to advance sleep and circadian research that improves medicine, public health, and the safety of the American public. We hope you join us in our efforts.

Marishka K. Brown, Ph.D.
Director, National Center for Sleep Disorders Research
National Institutes of Health
Executive Summary

In 1993, the U.S. Congress established the National Center on Sleep Disorders Research (NCSDR), located within the National Heart, Lung, and Blood Institute (NHLBI), because of the tremendous toll sleep deficiency and sleep disorders had begun taking on productivity, morbidity, and mortality. Part of the legislation mandated the development of a comprehensive National Sleep Research Plan [1].

Although sleep is a critical requirement for overall health and well-being across the lifespan, some 30–40% of U.S. adults and 65–80% of teens report sleep deficiency (e.g., insufficient sleep, irregular timing of sleep, poor quality of sleep) each year, according to the Centers for Disease Control and Prevention. Scientific evidence has consistently linked sleep deficiency and sleep disorders to disease pathology in almost every tissue in the human body. An economic analysis of health costs associated with sleep deficiency — including the burden of disease, accidents, and lost productivity — indicated losses that amounted to nearly $411 billion a year, or about 2.3% of U.S. gross domestic product [2].

Since the NCSDR was established, the sleep and circadian fields have advanced from basic knowledge about how sleep impacts safety, to a deeper understanding of sleep disorders. Research has also explored the genetics of narcolepsy and the heterogeneity of sleep apnea, as well as the multisystem effects of sleep and sleep deficiency on health and disease.

Major scientific accomplishments, particularly the discovery of molecular mechanisms controlling circadian rhythms — which earned the 2017 Nobel Prize in Physiology or Medicine [3] — have illustrated how basic mechanistic studies and medicine can help promote health and well-being. However, investigation of sleep and circadian biology across the basic, clinical, and translational science spectrum is necessary to further these advances with high translational value. This work will be critical to improving our scientific knowledge, transforming health care, and advancing public health and safety and the well-being of the nation. Foundational to this science will be the development of a diverse and interdisciplinary workforce that can stimulate the application of sleep and circadian scientific advances into crosscutting areas.

In developing the 2021 NIH Sleep Research Plan, the following Strategic Goals were identified, each of which are high-priority research areas that list specific opportunities for investigation:

**Goal 1:** Elucidate the Sleep and Circadian Mechanisms Underlying Health and Disease

**Goal 2:** Improve the Treatment of Sleep and Circadian Disorders and Reduce the Risk Associated with Sleep Deficiency and Circadian Misalignment

**Goal 3:** Identify Gaps and Opportunities to Accelerate the Clinical Implementation of Sleep and Circadian Research and Protect Public Health

**Goal 4:** Advance the Scientific Understanding of Sleep and Circadian Contributions to Health Disparities in Diverse Populations, and Their Different Impacts on the Public Safety of These Populations

**Goal 5:** Foster the Development of a Strong and Diverse Workforce for Sleep and Circadian Research
In addition, nine Critical Opportunities (CO) related to the strategic goals are featured. These COs were deemed timely and actionable, with potential for the highest transformative value to medicine and public health:

<table>
<thead>
<tr>
<th>CO</th>
<th>Description</th>
<th>Goal(s)</th>
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<tbody>
<tr>
<td>CO1</td>
<td>Identify biomarkers in sleep and circadian physiology to indicate the severity of medical conditions and the effectiveness of therapeutic interventions. (Goal 1)</td>
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<td>CO2</td>
<td>Elucidate the significance of sleep and circadian biology to immune function and the microbiome. (Goal 1 and Goal 2)</td>
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<td>CO3</td>
<td>Elucidate the relationships between sleep and circadian rhythms and dementia pathobiology and clinical outcomes, including Alzheimer’s disease and related dementias. (Goal 1 and Goal 4)</td>
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<td>CO4</td>
<td>Identify the neurobiological mechanisms underlying the perception of sleep quality, sleepiness, and fatigue. (Goal 1)</td>
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<td>CO5</td>
<td>Develop chronotherapeutic approaches to prevent and treat chronic diseases. (Goal 3)</td>
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<td>CO6</td>
<td>Develop tools and/or methods for the early prediction, detection, and treatment of sleep deficiency and sleep and circadian disorders in children and adolescents to promote lifelong health and well-being and prevent disease. (Goal 1 and Goal 3)</td>
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<td>CO7</td>
<td>Standardize measurements and data and demonstrate how dissemination and implementation of high-quality care for sleep and circadian disorders can be improved by data science approaches in adaptive healthcare systems. (Goal 2, Goal 4, and Goal 5)</td>
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<td>CO8</td>
<td>Embed omics-based approaches in real-world healthcare settings to facilitate personalizing treatments and cures for sleep and circadian rhythm disorders. (Goal 2, Goal 3, and Goal 5)</td>
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<td>CO9</td>
<td>Identify people-driven approaches to improve awareness of sleep and circadian rhythms and promote healthy sleep behaviors for the benefit of public health and safety. (Goal 3 and Goal 4)</td>
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The plan incorporates crosscutting NIH priorities that address minority health and health disparities, sex as a biological variable, inclusion across the lifespan, the opioid epidemic, and how the loss of sleep health may exacerbate the risk and outcome of infectious diseases such as COVID-19. The plan also covers the development of personalized treatments for sleep and circadian disorders. That said, the opportunities identified in this research plan are not meant to be inclusive of every important research topic in sleep and circadian biology, and they do not preclude the scientific exploration of any other significant topic in this field.
Introduction

Sleep and circadian rhythms profoundly influence the crucial functions of nearly every cell and organ in the body. Understanding how this internal body clock regulates the timing of sleep and wakefulness — as well as myriad other essential physiological functions — presents unique opportunities. With the many tools and approaches available today, researchers now have the potential to develop interventions that impact a broad range of health concerns, from mental well-being and resilience to disease, to social determinants of health and public safety.

The 2021 NIH Sleep Research Plan is based on a set of research needs and opportunities identified with input from researchers, public representatives, NIH workshop participants, and programmatic staff. The scientific recommendations discussed herein are based on discussions with the Sleep Disorders Research Advisory Board (SDRAB) (Appendix A), members of the public attending SDRAB meetings, and representatives of NIH extramural programs participating in the NIH Sleep Research Coordinating Committee (SRCC) (Appendix B).

Generating high-value scientific knowledge in sleep and circadian research — from basic mechanistic biology to clinical translation — will lead to new avenues for curing disease and promoting health, well-being, and safety. Taking advantage of opportunities in these still-developing sleep and circadian disciplines will require innovative strategies that will result from effective training of a diverse, interdisciplinary scientific workforce.

This plan presents a vision that advances the mission of the National Center on Sleep Disorders Research and builds on almost three decades of unparalleled success by sleep and circadian researchers. The five strategic goals, research priorities, and tactics, all demonstrate how the sleep and circadian sciences can advance medicine and promote public health. Additionally, the nine critical opportunities highlight the potential to broaden the landscape of biomedical sciences in the context of sleep and circadian research.
The NCSDR Overarching Mission:
To promote sleep and circadian scientific advances with high translational value to improve our scientific knowledge, transform health care, and advance public health and safety and the well-being of the nation.

Strategic Goals
The strategic goals are long-term objectives that, if reached, have the potential to change the landscape of sleep and circadian research. They set research priorities and benchmarks that will improve our scientific knowledge, transform health care, and advance public health and safety and the well-being of the nation.

- **Advance Scientific Knowledge**
  - Chronobiology
  - Neurophysiology
  - Gene Expression
  - Epigenetics
  - Proteostasis

- **Transform Health Care**
  - Epidemiological Risks
  - Risk Stratification
  - Chronomedicine
  - Clinical Interventions
  - Patient-centered Strategies

- **Advance Well-being**
  - Social Determinants Disparities
  - Individual and Community-based Interventions

- **Improve Public Health & Safety**
  - Prevention Worksites
  - Schools
  - Solid-state Lighting
  - Transportation
  - Housing

- **FOSTER A STRONG AND DIVERSE WORKFORCE**
GOAL 1: 
Elucidate the Sleep and Circadian Mechanisms Underlying Health and Disease

National surveillance data from the Centers for Disease Control and Prevention estimates that more than 30% of U.S. adults and more than 65–80% of teens nationwide report sleep deficiency (e.g., insufficient sleep, irregular timing of sleep, poor quality of sleep). Chronic diseases and social determinants of health (e.g., race and ethnicity, housing and the built environment, lifestyle and occupational factors, psychosocial stressors) are all associated with sleep deficiency and circadian misalignment — the mistiming of internal biological cycles relative to external environmental or behavioral factors. Identifying mechanisms underlying sleep and circadian biology is essential for predicting responses to influences that might disrupt regulation of these systems and ultimately lead to early detection of health-to-disease transitions. These mechanistic insights could enable earlier and more precisely targeted interventions that could leverage methodological and technological advances in optogenetics, functional brain imaging, wearable devices, and informatics. Ultimately such refined interventions could be implemented at a population level.

This research would:

• Better define the biological processes involved in maintaining sleep and circadian health to enable early detection of their disruption and the consequent transition to disease.

• Promote health and resilience against disease by leveraging these processes.

GOAL 1: High-Priority Research Areas

BASIC MECHANISTIC STUDIES

• Identify non-neuronal cellular and molecular mechanisms, and inter-organ alignment and crosstalk underlying sleep and circadian biological processes.

• Identify the complex interactions of circadian rhythms across various organ systems through computational and mathematical modeling (systems biology) and identify emergent phenomena that influence health and disease.

• Explore mechanisms underlying the bidirectional relationship of the aging process and circadian rhythms.

• Advance mechanistic understanding of the pathways modulating pain, reward, sleep, and circadian rhythms to identify new therapies.
GOAL 1: High-Priority Research Areas (Continued)

PATHOGENIC EFFECTS OF SLEEP AND CIRCADIAN DISRUPTION

• Determine the brain mechanisms and effects of sleep and circadian rhythms on development, illness course, and treatment of mental health disorders, and identify the genetic basis of such interactions.

• Explore the mechanistic basis for circadian rhythm and/or sleep disruption and cancer risk.

• Identify the effects of sleep disruption on reproductive development and function.

• Explore the role of sleep and circadian rhythms in blood brain barrier regulation as it affects drug efficacy.

• Explore the genetic, epigenetic, molecular, cellular, and systemic mechanisms that determine sex-related differences in sleep and circadian disorders.

• Define the sex-related differences in sleep quality and quantity in relationship to autoimmune disease.

• Identify the neural mechanisms and bidirectional interactions between sleep deprivation or disruption, and mental health disorders, including emotional dysregulation and mood disorders.

IDENTIFICATION OF DISEASE PROCESSES AND BIOMARKERS

• Identify sleep and circadian influences on the biology underlying obesity and cardiometabolic risk in humans and develop preclinical models to better tailor interventions in clinical-translational studies.

• Understand the interplay between intermittent hypoxia, sympathetic activation, the microbiome, and endogenous stem/progenitor cells, and how this interplay contributes to disease progression.

• Develop and test preclinical models of sleep and circadian disturbances in relation to critical illness (e.g., sepsis) and identify novel targets for drug discovery and therapeutic management.

• Explore single-cell analytics to understand the cellular phenomena of sleep and circadian rhythms and enable discovery of surrogate biomarkers for sleep and circadian disorders.

LONG TERM ENVIRONMENTAL AND POPULATION EFFECTS

• Understand the effects of developmental alcohol exposure on sleep patterns later in life, and the mechanisms of alcohol-related sleep disorders.

• Examine mechanisms underlying sleep-related pathology contributing to risk for Alcohol Use Disorder (AUD) and the role of persistent sleep problems emerging during abstinence from alcohol use in relapse.

• Elucidate multilevel and multifactorial causal pathways for disparities in sleep and circadian disorders. For example, examine the role of sociocultural and physical/built environmental determinants on population sleep disparities.

• Explore the effects of environmental exposures (e.g., particulates, pathogens, temperature, light exposure, humidity) on sleep and circadian rhythms, and downstream consequences on health, such as for poor diet, physical inactivity, sedentary behaviors, organ dysfunction and disease.

• Explore the effects of substance use such as alcohol, cigarettes, and illicit drugs (e.g., methamphetamine, cocaine, heroin, fentanyl) and misuse of psychotherapeutic drugs (e.g., prescription opioids and stimulants) and how disrupted sleep contributes to addiction.
GOAL 2:
Improve the Treatment of Sleep and Circadian Disorders and Reduce the Risks Associated with Sleep Deficiency and Circadian Misalignment

The negative impact of sleep and circadian disorders, and sleep deficiency outside of a disorder, has widely been recognized as a growing economic and public health concern. Addressing the problem requires the coordinated and well-planned prioritization of research. This entails developing and implementing tailored approaches, designed and targeted to populations with diverse characteristics. Such efforts could complement primary and secondary prevention approaches at the individual level.

This research would:

• Bring effective treatments and cures to patients with sleep and circadian rhythm disorders.
• Identify strategies that lead to long term adherence to these interventions/treatments.
• Advance understanding of sociocultural and physical/built environmental factors that may impact these interventions.

GOAL 2: High-Priority Research Areas

ROLE OF SLEEP AND CIRCADIAN DISORDERS IN DISEASE

• Examine the effects of sleep-disordered breathing treatment on cardiometabolic outcomes and the mediator/moderator role of the gut microbiome in effecting such cardiometabolic outcomes.
• Elucidate the relationship between circadian biology, sleep health, and the timing of food intake on cardiometabolic health and obesity.
• Improve understanding of the influence of sleep and circadian rhythms on pain, addiction, and recovery from addiction across the lifespan.
• Understand the effect of sleep and circadian disruption on critically ill patients.
• Understand the impact of sleep and circadian rhythms and their disorders on traumatic brain injury through observational and intervention-based research studies.

IMPROVEMENTS IN ASSESSMENT

• Understand the cardiorespiratory interactions of therapeutic approaches for sleep-disordered breathing in patients with underlying cardiac, respiratory, or blood disorders.
• Develop screening and treatment approaches for sleep-disordered breathing in the perioperative setting to improve patient outcomes and reduce healthcare costs.
• Identify the pathobiology of sleep-disordered breathing (SDB) during pregnancy and the effect of treating SDB during pregnancy on maternal and infant morbidity and mortality.
• Examine the effect of sex/gender on treatment and diagnostic pathways for sleep disorders and related outcomes.
GOAL 2: High-Priority Research Areas (Continued)

EFFECTIVENESS RESEARCH FOR TREATMENT OF SLEEP DISORDERS

- Identify optimal and personalized interventions for individuals with obstructive sleep apnea through comparative effectiveness trials of available therapies (e.g., positive airway therapy versus dental devices or implantable hypoglossal stimulators).

- Determine whether interventions for SDB can decrease morbidity and mortality.

- Determine what level of intervention for SDB yields optimal outcomes and promotes adherence.

- Develop and test interventions to improve sleep and circadian rhythms in critically ill patients and assess short- and long-term outcomes to distinguish causal influence from associations and epiphenomena.

- Identify the effect of simultaneously or sequentially treating sleep and circadian rhythm disorders in patients with comorbid medical, behavioral, and psychiatric conditions, and explore the effect of such treatment approaches on patient- and system-level outcomes.

- Conduct long-term comparative effectiveness research on medications versus cognitive behavioral therapy to treat insomnia.

- Conduct comparative effectiveness research on complementary and alternative approaches for insomnia versus cognitive behavioral therapy, including various modalities of delivery, such as telemedicine, digital and mobile health.

NOVEL THERAPEUTIC APPROACHES

- Develop and test multimodal medication and behavioral approaches targeting patients and providers to improve sleep and circadian rhythms.

- Develop and test innovative approaches to improve healthcare coordination in patients with SDB.

- Investigate the mechanisms by which complementary and integrative health approaches (such as botanicals, probiotics/microbials, acupuncture and other manual therapies, yoga, meditation) impact sleep and/or circadian biology and outcomes.

- Improve adoption by providers of nonmedication approaches (e.g., light therapy) to improve circadian rhythms in patients with comorbidities and study the effects on measurable clinical outcomes.

- Develop novel approaches (e.g., behavioral interventions) that are not limited by poor adherence to improve treatment for individuals with sleep and circadian disorders.

- Study sleep interventions and treatment of sleep disorders as an approach to improve pain control and reduce reliance on pain medications.

- Develop and test novel therapies for sleep and circadian rhythm disorders that meet the definition for orphan medical conditions (e.g., narcolepsy, non-24-hour sleep-wake disorder [non-sighted and sighted], fatal familial insomnia).

MODIFIERS OF TREATMENT EFFECTIVENESS

- Understand mechanisms that underlie resilience and/or susceptibility to risks associated with circadian sleep disorders and sleep deficiency.

- Understand the impact of medications that treat mental illnesses on sleep regulation and the impact of insomnia treatments on mental illness symptoms, including suicidal ideation and behavior.
GOAL 3:
Identify Gaps and Opportunities to Accelerate the Clinical Implementation of Sleep and Circadian Research and Protect Public Health

Rapid advancements in informatics, targeted use of electronic health records (EHRs), and telemedicine in the delivery of health care hold great promise in addressing the need for quality health care for all. The immense potential inherent in digital health, which includes mobile health (mHealth) technologies to transform health care, personal health management, and basic health research offers scalable options for treating sleep deficiency and sleep and circadian disorders at a population level. Digital health could be particularly relevant to underserved populations as cell phones and Internet access become more ubiquitous — reducing barriers that limit access to quality health care and providers. Intriguingly, gamification of health care in under-resourced communities is an underexplored area that could have a global impact. By leveraging information technology and data science to deliver quality health care through innovative approaches, the research and medical communities can dramatically change the healthcare landscape. Evidenced-based medicine is needed to guide implementation of these novel approaches into healthcare systems and health services research. Dissemination and implementation trials will be critical to inform these new directions.

This research would:

- Incorporate sleep and circadian research into healthcare delivery to enable natural experiments and continuous improvements in healthcare delivery.
- Reduce barriers and promote facilitators for more widespread, efficient, and effective healthcare delivery.
GOAL 3: High-Priority Research Areas

INNOVATIONS IN DATA COLLECTION AND APPLICATION TO TREATMENT

• Develop common measures and protocols to collect omics and sleep and circadian data and integrate that data with EHRs, databases, and platforms to better predict healthcare utilization, transitions of care, and cost effectiveness.

• Identify patient, provider, and system-level factors that influence the detection, testing, and self-management of sleep and circadian disorders.

• Develop and implement clinical decision support systems that can be integrated into EHRs to provide high-quality care to patients with sleep and circadian disorders. These efforts can also reduce geographic and provider-based variations in practice, particularly in low-resourced clinical settings.

• Incorporate the Alcohol Use Disorders Identification Test (AUDIT) or AUDIT-Consumption (AUDIT-C) into sleep screening to identify patients who are hazardous drinkers or have active AUD and are at risk for developing alcohol-induced sleep disorders and/or SDB to improve patient outcome and reduce healthcare costs.

IMPROVEMENTS IN CLINICAL AND IMPLEMENTATION TRIAL DESIGNS

• Explore methods to circumvent “healthy volunteer bias” in conventional observational cohorts, clinical trials, registries, and repositories, and improve representation among populations that are typically under-represented (NIH-defined under-represented) such as older adults ages 65 and older, and individuals with disabilities.

• Utilize/develop informatics-based approaches to determine areas of clinical interest and implementation requirements for appropriate implementation science trial design and execution.

• Perform cost-effectiveness research on the treatment of sleep and circadian disorders in integrated healthcare systems, with an emphasis on meaningful patient outcomes (e.g., health-related quality of life, hospitalization, morbidity, and mortality).

• Promote the dissemination and implementation of a stepped-care approach for the treatment of SDB in patients with prehypertension or treatment-resistant hypertension.
**GOAL 4:**
Advance the Scientific Understanding of Sleep and Circadian Contributions to Health Disparities in Diverse Populations, and Their Different Impacts on the Public Safety of These Populations

Sleep health disparities (SHDs) are differences in one or more dimensions of sleep health (duration, efficiency, timing, regularity, alertness, and quality) — on a consistent basis — that adversely affect designated disadvantaged populations. The designated health disparity populations include American Indians/Alaska Natives, Asian Americans, Blacks/African Americans, Hispanics/Latinos, Native Hawaiians and other Pacific Islanders, sexual and gender minorities, the socioeconomically disadvantaged; and those living in underserved rural areas. Pronounced SHDs can be found among these populations in the U.S. The incidence and prevalence of sleep deficiencies at a population level are influenced by many of the same determinants that influence other health outcomes with known disparities. Understanding the factors that contribute to these disparities in sleep and circadian rhythms-related disease risk will inform improved approaches for personalized medicine. Thus, a nuanced integration of health disparity causal pathways and sleep and circadian-related mechanisms, tailored for the specific population(s) and sensitive to the sociocultural context(s), is needed to understand and address SHDs.

Strategies to address SHDs were identified by the research community and described in detail in an article, “A workshop report on the causes and consequences of sleep health disparities.” Those strategies include: a) develop and promote integrative research on SHDs, b) investigate the causes and health consequences of SHDs, and c) develop interventions to address SHDs.

**This research would:**

- Improve sleep health by targeting populations that experience health disparities.
- Enable more patient-centered approaches to prevent, diagnose, and treat sleep and circadian rhythm disorders.
- Advance effective public health and safety policies that address SHDs.
GOAL 4: High-Priority Research Areas

EDUCATION AND AWARENESS

- Develop education-based studies to increase societal awareness of the importance of consistent sleep and circadian rhythms, as well as adequate nutrition and physical activity, to promote optimal health among underserved U.S. populations.

- Develop studies to investigate how increased social awareness of the effects of short- and long-term chronic drinking on sleep quality impact behavior.

- Improve understanding of sex and gender differences in sleep quantity and quality in relation to demographic and social determinants of health.

- Understand the relative contribution of environment/geolocation, racial discrimination, and adverse childhood experiences on sleep and sleep disorders across race/ethnicity.

- Enable data-driven health policies aimed at promoting consistent sleep and circadian rhythms and management of sleep and circadian disorders in populations burdened by health disparities.

- Enable community-based research to facilitate comparative-effectiveness, dissemination, and implementation research in sleep and circadian disorders.

- Develop studies to investigate how increased awareness of sleep and circadian rhythms disorders play a role in the health and well-being of underserved populations, including shift workers and patients with sleep and circadian rhythm disorders.

- Develop multilevel strategies to disseminate and implement guideline-based and high-quality care for sleep and circadian rhythm disorders in populations with existing health disparities.

POPULATION AND ENVIRONMENTAL ANALYSES

- Study the characteristics of social and physical environments in schools, colleges, healthcare facilities, and workplaces that promote good sleep and aligned circadian rhythms, noting the effects on the health and health-related quality of life, healthy development and behaviors and mental health in under-served populations across all life stages.

- Identify and measure qualitative and quantitative measures that reveal barriers to and facilitators for promoting equity in healthcare delivery for sleep and circadian disorders.

- Investigate racism, sexism, and other forms of discrimination as a major contributor to cumulative chronic stress and a driver of disparities in sleep and circadian disorders.

- Understand the relative contribution of environment/geolocation, racial discrimination, and adverse childhood experiences on sleep and sleep disorders across race/ethnicity.

- Gain understanding of geographic variability in healthcare delivery to patients with sleep and circadian disorders, as well as determine how such variability influences health and well-being.

- Develop and test “real-world” interventions through novel, system-level redesigns aimed at promoting improved sleep and circadian rhythms in shift workers, and study their effects on health, well-being, and patient and public safety, especially in populations that experience SHDs.

- Integrate sleep and circadian research into big-data analytics and leverage social media metrics coming from beyond the biomedical realm to present research such that findings might be understood and adopted by those with SHDs.
GOAL 4: High-Priority Research Areas (Continued)

- Explore the effect of sleep and circadian disorders in the workplace with respect to absenteeism, presenteeism, costs to employers, and workplace safety.

- Develop novel approaches for multi-modal detection of sleepiness and fatigue (including biomarkers) in transportation and related industries.

- Develop and implement mechanisms for preventing fatigue and sleepiness related accidents in homes, transportation, health care, and other industries.

- Study the multifactorial relationships between social, environmental, and policy level factors (e.g., discrimination, noise) and sleep and circadian health among U.S. underserved populations.

IMPROVING TREATMENTS FOR POPULATION EXPERIENCING DISPARITIES

- Develop multilevel interventions that incorporate social and environmental determinants of health to address disparities in sleep and circadian rhythms health care.

- Leverage information technology and data science to promote health equity in prevention, identification, and treatment of populations experiencing health disparities.

- Develop interventions for healthcare settings that serve socioeconomically disadvantaged and rural populations.

- Develop and test endotyping, phenotyping and diagnosis protocols to advance treatment of gestational OSA in underrepresented women.

- Validate commonly used sleep metrics in populations experiencing disparities, and/or develop new sleep metrics that will be valid in these populations.

- Develop transdisciplinary approaches, including mobile health technologies, to address sleep health disparities in sleep disorders by engaging not-well-reached (priority) populations, enabling interventions, and developing outcomes assessments.

Aligning with an essential focus of NIH, the health of women is also a priority in sleep and circadian research. Sex differences in sleep emerge at a very early age and as time passes, may be affected by variations in reproductive hormones, stress, depression, aging, and role transitions, including changes in sleep related to menstruation, pregnancy, post-childbirth, and menopause. Women report poorer sleep quality and have higher risk for insomnia than do men and special considerations that acknowledge sex as a biological variable should be made when considering treatment.
GOAL 5:
Foster the Development of a Strong and Diverse Workforce for Sleep and Circadian Research

Building a diverse scientific workforce, as well as recruiting and retaining currently active researchers in the fields of sleep and circadian biology, are high priorities. The diverse workforce includes all groups as highlighted by the Notice of NIH’s Interest in Diversity (NOT-OD-20-031), as well as people with different backgrounds and perspectives. Diversifying the sleep and circadian workforce should start as early in the education pipeline as possible to ensure that talented individuals can engage in sleep and circadian research at the beginning phases of their careers. The rapid growth of this area of investigation, with its inclusion of basic, clinical, and population sciences, affords investigators access to a variety of research shared by few other scientific disciplines. The increase in both the number of awards and the number of Institutes, Centers, and Offices across NIH that fund sleep and circadian research signifies its evolution and expansion into new areas, as well as its potential for further growth. These advancements provide new opportunities for scientists from a variety of backgrounds to engage in sleep and circadian-related research, including data science, implementation research, public health, nursing, medicine, and bioinformatics — all of which could advance human health and safety.

TACTICS for Addressing Research Areas in Sleep and Circadian Research

Methodological and technical barriers can delay innovation in both the science and practice of translating sleep and circadian rhythms into medicine and public health. Solving such issues can have a transformative effect on the field and improve the ease and pace of research in sleep and circadian rhythms. Methodological and technical innovations will aid in advancing sleep and circadian sciences.

**TACTICS**

- Develop, test, and validate new cellular and animal models of health and disease states of sleep and circadian rhythms, and develop consensus on the advantages and disadvantages of such models.
- Develop, validate, and set standards for wearable devices that can measure sleep and circadian rhythms, and integrate such measures with other physiological data into EHRs.
- Utilize artificial intelligence techniques to enable predictive modelling and the interoperability of multidimensional sleep and circadian rhythms data; improve disease surveillance; identify positive deviance; enhance treatment adherence; promote early and effective engagement of patients, public and stakeholders; and support platforms for comparative effectiveness research and clinical decision support systems.
- Develop accessible and harmonized data science approaches to better understand circadian contributions to health and disease.
- Promote inclusion of more diverse patient populations with circadian rhythm and sleep disorders in research.
Critical Opportunities (CO)

This plan identifies timely and actionable research approaches with the potential to significantly impact sleep, circadian, and biomedical sciences that were identified across the translational spectrum — from knowledge generation and discovery science to medicine and public health. These opportunities map to multiple strategic goals and were selected as examples that inform the overall research agenda. These opportunities do not exclude other research directions or limit the consideration of any investigator-initiated line of study.

**CO1: Identify biomarkers in sleep and circadian physiology to indicate the severity of medical conditions and the effectiveness of therapeutic interventions.**

Molecular and cellular indicators of normal biological processes, disease processes, and responses to an exposure or intervention (biomarkers) are critical to translating advances in sleep and circadian science, as well as medical and public health applications. Objective tools to efficiently measure the magnitude of genomic and clinical abnormalities associated with sleep deficiency and poor circadian health enable the discovery of potentially modifiable risk factors, predict sleep and circadian-related susceptibility to disease, and provide the validated assessments of therapeutic efficacy.

Analyses of physiological and pathological readouts indicate the close interrelationship between physical and mental health and sleep and circadian function. Existing computational technologies are designed to probe these readouts systematically for indicators of sleep or circadian function and promising biomarkers of mood disorders and emotional dysregulation. These efforts will require multiomic data resources, which include daily patterns of metabolic profiles, epigenomics, and protein and RNA expression patterns. Advances in collection and accessibility of these data could permit development of sleep and circadian biomarkers that might improve evaluation and treatment of sleep-related risk and health outcomes across the lifespan.

**CO2: Elucidate the significance of sleep and circadian biology to immune function and the microbiome.**

Inflammatory homeostasis and the immunological response to damaged or unhealthy cells are closely coupled to preservation of sleep and circadian rhythms that sustain cellular physiology. The number of immune cells, such as lymphocytes and antigen presenting cells, and the expression of cytokines increase to maximal values during sleep and decrease during wakefulness. Because this homeostasis cannot be maintained during disturbances in sleep and circadian function, an array of abnormalities in innate and adaptive immunity may arise. Resilience to infection gets reduced, damaged, or unhealthy cells fail to be removed, and inflammatory equilibrium becomes disrupted. Sleep and immunity are also bidirectionally linked: the release of inflammatory factors promotes deep slow-wave sleep, which is critical to optimal host defense.

Scientists can now map circadian rhythms in previously unimaginable detail due to technological advancements in the 24-hour measurement of gene activity and proteomics in the microbiome.
Understanding these multi-system interactions in normal biological processes would allow us to define health and measure its perturbation by the environment, pathogens, or early disease processes more clearly. The ability to detect and prevent abnormalities associated with early disease processes could accelerate the development of new therapies and strategies for health promotion and resilience.

**CO3: Elucidate the relationships between sleep and circadian rhythms and dementia pathobiology and clinical outcomes, including Alzheimer’s disease and related dementias.**

Changes in sleep and circadian rhythms typically occur with aging; however, there are distinct differences between the changes that occur in healthy aging and those associated with neurodegenerative diseases. Over the past decade, seminal findings linking sleep and circadian biology with neurodegeneration have offered compelling evidence underscoring the importance of sufficient sleep for optimal brain health. The discovery of the role of the glymphatic system in clearing accumulated neurotoxic waste products from the brain during sleep, and the strong association between sleep deficiency, sleep disorders and the vasculature, are key examples that not only highlight a new role for sleep in maintaining brain health at the individual level, but also demonstrate the impact of sleep and circadian sciences at the population and societal levels. Neurodegenerative diseases, such as Alzheimer’s disease and Parkinson’s disease, and traumatic brain injury are all associated with disrupted sleep and circadian rhythms. More importantly, evidence of the bidirectionality of this relationship is mounting. Not only do these conditions impact sleep, but sleep-wake and circadian disruptions can also exacerbate neurodegenerative pathologies.

**CO4: Identify the neurobiological mechanisms underlying the perception of sleep quality, sleepiness, and fatigue.**

Improved understanding of the neurobiological mechanisms underlying sensations of sleepiness and fatigue, or the urge to sleep, could be transformative not only for sleep and circadian sciences, but for other fields. Emerging technologies permitting more precise brain and molecular imaging, combined with the recognition of the public health impact of widespread and chronic sleep loss, sleepiness, and fatigue, may offer new solutions to an unyielding challenge. fMRI studies indicate that sleep and circadian rhythms modulate the activity of brain regions underlying emotional regulation, cognitive function, coping, and interoceptive perception of pain and fatigue. For example, the study of interoception, which refers to the representation of the internal world, and includes the processes by which an organism senses, interprets, integrates, and regulates internal signals, is extremely relevant to sleep and fatigue. Both sleep and interoception are tightly connected to physical and mental well-being, with complex, dynamic relations between sleep and sensory processes within each modality of interoception (e.g., thermoception, nociception, visceral sensations, and subjective feelings about these sensations). A better understanding of these interrelations may facilitate management of chronic pain, insomnia, and other sleep and mental disorders. Additionally, identifying the similarities and differences in the underlying causes of fatigue as a symptom in many different disease conditions, and the role of sleep and circadian mechanisms in these conditions, is also of great importance. Psychological mechanisms and cultural factors also influence perception, and exploration of their impact on sleep quality, sleepiness, and fatigue are equally important and should be considered.
CO5: Develop chronotherapeutic approaches to prevent and treat chronic diseases.

The broad influences of natural, physiological rhythms on human cellular, molecular, and emergent systems suggests that further understanding of these rhythms might be leveraged to treat chronic conditions, including obesity, cardiovascular disease, metabolic and respiratory diseases, cancer, rheumatoid arthritis, and mental health disorders. Applying the insights gained to develop or refine chronotherapeutic approaches, such as adjusting the timing of treatments to circadian rhythms, could enhance their efficacy. Research has shown that medical treatments for conditions such as asthma, hypertension, cancer, and cardiovascular disease work best depending on the time of day they are administered. For example, better drug effectiveness for central nervous system disorders may be determined by considering how circadian regulation of the blood-brain barrier influences its permeability. Additionally, correcting disturbed circadian rhythms, such as by advancing phase delays with the use of sleep restriction and light therapy, can be an important component in the treatment of some mental disorders, including seasonal affective disorder and peripartum depression. Optimizing the timing of medication administration in accordance with circadian rhythm profiles could maximize efficacy and minimize toxicity or side effects. Such consideration may create paradigm shifting approaches to prevent or treat major medical conditions.

CO6: Develop tools and/or methods for the early prediction, detection, and treatment of sleep deficiency and sleep and circadian disorders in children and adolescents to promote lifelong health and wellbeing and prevent disease.

Sleep is critical to pediatric and adolescent development and daily functioning and impacts performance and health trajectories. The effects of insufficient sleep in children may persist into adulthood, and this has wide-ranging implications for health and life outcomes. Recent findings suggesting that epigenetic and metabolic effects of sleep deficiency and circadian abnormalities may be persistent and enduring across the lifespan provides a mechanistic basis. Additionally, maternal sleep deficiency has been linked to increased adiposity in offspring, and alterations in postnatal neurodevelopment, emotional regulation, and metabolic and cardiac risks have been associated with childhood sleep deficiency. Sleep deficiency and untreated sleep disorders can cause increases in blood pressure, atherosclerotic inflammation, and cardiometabolic disease risks at all ages.

Studies have also linked housing and neighborhood conditions to sleep loss. Sleep is particularly reduced in low-income and developmentally delayed children ages 3 to 6, and thus contributes to known health disparities that have long-term consequences. Evidence is emerging that environmental factors at the household and neighborhood level can also alter children’s sleep. Social vulnerability, the negative effects of external stressors on health at the community level, and adverse childhood experiences, which are stressful or traumatic life events that occur during the first 18 years of life, both have been linked to sleep disturbance in adults. Investigating the impact of sleep and circadian disruption early in life, and how these exposures affect disease and health trajectory across the lifespan, could help to identify opportunities for early interventions to prevent disease.
CO7: Standardize measurements and data and demonstrate how dissemination and implementation of high-quality care for sleep and circadian disorders can be improved by data science approaches in adaptive healthcare systems.

The application of artificial intelligence (AI) is becoming increasingly common in the healthcare setting. Leveraging analytic approaches for big data by incorporating complex information from multiple sources — EHRs cohorts, clinical research studies, registries, smartphones, and wearable devices, for example — could be used to advance our understanding of sleep and circadian disorders. But importantly, these approaches could also provide information about prevalence of these disorders, assist in the personalization of treatments, improve the allocation of resources, and inform healthcare policies. AI approaches could also be used to better understand sources of inequity in health care and health research related to sleep and circadian disorders. However, a major challenge is the lack of representation of diverse populations in big datasets. As innovation is not typically done through a health equity lens, it will be critical for research communities to consider this perspective in any approach that is developed. Recognizing the importance of information management and data sharing practices in publicly funded research projects, the NIH has announced more expansive policies aimed at improving transparency, reproducibility, and availability of scientific data.

CO8: Embed omics-based approaches in real-world healthcare settings to facilitate personalizing treatments and cures for sleep and circadian rhythm disorders.

Personalized medicine and its challenging mission of harnessing patient-level data to refine (or personalize) care from diagnosis and treatment to monitoring, remains a prominent goal in medical research. One pathway to personalizing medicine is through an omics-based approach — that is, leveraging the various methods and tools used to investigate the structures, functions, activities, and interactions of different molecules within an organism.

Technological breakthroughs have been achieved by combining multiple “omics” approaches and artificial intelligence platforms and have revealed intriguing possibilities. Pragmatic research approaches within adaptive healthcare systems that continually improve care through daily learning and evaluation could transform healthcare delivery — not only within sleep and circadian medicine, but also in other medical fields. Furthermore, including the collection and timestamping of biological samples during normal clinical workflows could create the foundational infrastructure for precision medicine in sleep and circadian sciences.

CO9: Identify people-driven approaches to improve awareness of sleep and circadian rhythms and promote healthy sleep behaviors for the benefit of public health and safety.

Placing people at the center of public health promotion is required to access not-well-reached populations for both primary and secondary prevention, treatment, and cures. This people-driven approach matters. The persistent barriers faced by under-represented minorities, rural populations, children, geriatric populations, individuals with disabilities, and other underserved groups, limit the ability of healthcare system-based
approaches to improve public health. SHDs remain an important focus in efforts to promote health equity, and they can be effectively addressed through community-engaged and people-based approaches. Moreover, the sizable costs associated with delayed care during advanced disease could be shifted to a preventative disease model through people- or community-driven approaches. Innovative educational approaches, as well as messaging similar to that used by the NIH Community Engagement Alliance (CEAL) Against COVID-19 Disparities, may be effective strategies for transferring health information and scientific advances from sleep and circadian biology researchers and healthcare providers to educators from diverse disciplines and underserved populations. Employing cognitive modeling approaches may also be considered when developing strategies that are people-driven.
Most of the acute effects of SARS-CoV-2 infection have been focused on the upper airway, lungs, and the cardiovascular system. Research has shown that the health and function of these systems are mediated by sleep and circadian rhythms biology. This relationship is further strengthened by recent evidence indicating that the risk of illness severity and death may be higher among COVID-19 patients with untreated sleep apnea. Furthermore, widespread reports of cognitive impairment in symptomatic patients indicate that the virus exerts direct and/or indirect effects on the central nervous system. The evidence for a neurological component to COVID-19 is further supported by documentation of the most common symptoms experienced by individuals after COVID-19: debilitating fatigue, difficulty breathing, cognitive dysfunction (or “brain fog”), and sleep disturbances, including insomnia. For example, evidence suggests that in some cases, respiratory failure and consequent mortality caused by the virus is not solely mediated through damage to the lungs but may also involve impairments to brainstem circuitry that regulates breathing.

Sleep and circadian biology are intrinsically tied to immune function and play a fundamental role in both mental and physical health. Extensive research has established that poor sleep and circadian misalignment undermines the immune system’s ability to fight infections, may impair the effectiveness of some vaccines and may delay recovery from critical illness. Early reports suggest that sleep is affected by SARS-CoV-2 infection, and fatigue/sleep deficiency is a common complaint from those experiencing post-acute sequelae of SARS-CoV-2 (PASC) or “Long COVID.” In addition to the significant impact on the health of the millions of individuals who have been infected by the virus, the COVID-19 pandemic has led to long-term behavioral, psychological, social, and economic consequences that will need to be addressed in the coming years. Adequate sleep duration, sleep quality, and regular sleep schedules are essential for coping with physiological and psychosocial stressors, such as the COVID-19 pandemic.

While accumulating research demonstrates that sleep disruption is a prevalent feature of COVID-19, research is urgently needed to determine whether sleep is directly involved in COVID-19 susceptibility, immune response, and related pathophysiology. Sleep deficiency is modifiable, and a potential target to improve COVID-19 prevention, management, and long-term outcomes.
### Emerging Opportunity: High-Priority Research Areas

- The role of sleep and circadian disruption in risk of infection and severity of acute COVID-19 across vulnerable populations.
- Sleep and circadian disruption as modifiers of COVID-19 pathobiology and risk of developing PASC.
- The long-term effects of COVID-19 on sleep and circadian biology.
- The contribution of sleep deficiency to COVID-19 long-term effects on the cardiovascular, pulmonary, and hematological systems, cancer, and other diseases.
- Understanding causes of fatigue as a symptom in many different disease conditions, and the roles of sleep and circadian mechanisms in exacerbating or mitigating fatigue in these conditions.
- The bidirectional relationship between alcohol misuse and sleep disruption as modifiers of COVID-19 outcomes.
- The effects of chronic alcohol drinking on sleep quality and their contributions to other symptoms, such as cognitive impairment, pain, and anxiety associated with PASC.
- How shift work and chronic sleep disruption combined with alcohol misuse and AUD, may worsen COVID-19 outcomes.
- The role of complementary and integrative health approaches (such as botanicals, probiotics/microbials, acupuncture, and other manual therapies, yoga, meditation) in the improvement or prevention of sleep and circadian disruption related to COVID-19.
- The role of sleep and circadian rhythm disruption in long-term chronic disease-related cognitive impairments such as PASC “brain fog” or “chemobrain.”
- Disruption of sleep in women – due to pregnancy and to factors such as COVID-19-related caretaking responsibilities or burnout.
- The impact of mitigation efforts in response to the COVID-19 pandemic on sleep, mental health, and well-being.
- The role of sleep and circadian disruption on the effects of COVID-19 across the cancer continuum, from cancer risk factors and diagnosis to treatment and survivorship.
- Modifications in the homeostatic system that prohibit sleep from reversing the fatigue associated with PASC.
Conclusion

The 2017 Nobel Prize in Physiology or Medicine was awarded for the discovery of the molecular mechanisms that control circadian rhythms in biological systems. This recognition reflects the convergence of advances in data science, trans-omics, computational biology, and functional brain imaging. All these have accelerated biomedical research efforts and increased our understanding of the molecular mechanisms of circadian rhythms and sleep in preclinical (animal) models. The accumulation of preclinical knowledge and methodological opportunities uniquely positions the field of sleep and circadian rhythms to translate these discoveries in ways that promote human health, prevent disease, and generate treatments and cures for patients. This new understanding of the biology of sleep and circadian rhythms presents enormous opportunities for further exploring the cellular and molecular biology of sleep, which in turn will help us to understand and target the pathobiological states that emanate from such systems. Given the cross-cutting and interdisciplinary nature of sleep and circadian rhythms, the investment of time and resources into sleep and circadian rhythms research will yield large rewards for the health and well-being of individuals and populations.
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