

**National  
Center  
On  
Sleep Disorders  
Research**

**NATIONAL INSTITUTES OF HEALTH  
SLEEP DISORDERS RESEARCH  
PLAN**

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## Table of Contents

3	Foreword
4	Executive Summary
6	Introduction
11	Goal 1 - Advance the understanding of sleep and circadian functions and of basic sleep and circadian mechanisms, in both the brain and the body, across the lifespan.
13	Goal 2 - Identify genetic, pathophysiological, environmental, cultural, lifestyle factors and sex and gender differences contributing to the risk of sleep and circadian disorders and disturbances, and their role in the development and pathogenesis of co-morbid diseases, and disability.
17	Goal 3 - Improve prevention, diagnosis, and treatment of sleep and circadian disorders, chronic sleep deficiency, and circadian disruption, and evaluate the resulting impact on human health.
19	Goal 4 - Enhance the translation and dissemination of sleep and circadian research findings and concepts to improve health care, inform public policy, and increase community awareness to enhance human health.
21	Goal 5 – Enable sleep and circadian research training to inform science in cross-cutting domains, accelerate the pace of discovery, and the translation of enhanced therapies from bench to bedside to community.
23	Appendix 1: Glossary
27	Appendix 2: NIH Participants
29	Appendix 3: Sleep Disorders Research Advisory Board
32	Appendix 4: Ad Hoc Consultants to Sleep Disorders Research Advisory Board

## Foreword

The National Center on Sleep Disorders Research (NCSDR) was established within the National Heart, Lung, and Blood Institute (NHLBI) via a provision of the National Institutes of Health (NIH) Revitalization Act of 1993. The NCSDR was mandated to:

- Conduct and support research, training, health information dissemination, and other activities with respect to a basic understanding of sleep and sleep disorders, including research on biological and circadian rhythms, chronobiology, and other sleep-related topics.
- Coordinate the activities of the NCSDR with similar activities of other Federal agencies, including the other components of the National Institutes of Health, and similar activities of other public and nonprofit entities.

Advances in sleep and circadian research during the last decade exemplify the NIH goal of fostering fundamental creative discoveries and innovation, and the application of that knowledge to ultimately protect health and prevent disease. Basic research on the genetics and molecular basis of sleep and circadian biology is opening up new avenues for investigation and potential therapeutic development. Biomedical research is also defining the role of sleep as a fundamental requirement of daily living with broad implications for the maintenance of health and well-being of people at all stages of life, the risk of disease, and public safety.

The 2011 update of the NIH Sleep Research Plan identifies new opportunities for continued advances in understanding the function of sleep to inform lifestyle choices and improve the opportunity of individuals to achieve their optimal health outcome. The plan was developed through an open process with the Sleep Disorders Research Advisory Board and with input from the public, academia and health care professionals. The plan recognizes that moving the research forward is a dynamic process that involves ongoing communication with researchers, health care providers, and private and public organizations. Research activities and stakeholders addressed by this plan can benefit from a wide range of NIH research, training and outreach programs. We are confident that these recommendations will continue to advance sleep and circadian biology research in health and disease.

Francis S. Collins, M.D., Ph.D.  
Director, National Institutes of Health

## Executive Summary

Sleep and circadian disturbances and disorders affect millions of Americans across all demographic groups. An estimated 25-30% of the general adult population, and a comparable percentage of children and adolescents, is affected by decrements in sleep health that are proven contributors to disability, morbidity, and mortality. As a result, sleep and circadian disturbances and disorders have been recognized by Congress and the Department of Health and Human Services<sup>1,2</sup> as high priority targets for basic and clinical scientific investigation. Three general categories of sleep and circadian disorders and disturbances have been described: 1) disorders of sleep and circadian rhythms; 2) sleep deficiency; and 3) environmental disruption of circadian functions. In addition to clinical sleep and circadian disorders, sleep deficiency and circadian disruption resulting from lifestyle factors are increasingly common societal problems that increase disease risk through complex pathways.

Advances sweeping across the spectrum of biomedical inquiry have transformed the sleep and circadian research landscape since the first NIH Sleep Disorders Research Plan was developed in 1996. The scientific domain is well-poised today to contribute knowledge advances and emerging technologies to the goals of understanding mechanisms of disease risk, accelerating translation from bench to bedside to community, and developing the evidence based evaluation of intervention effectiveness. Opportunities for research training exist in all areas of sleep and circadian biology and at multiple levels of the educational ladder. Scientific cross-fertilization and the development of an interdisciplinary workforce would stimulate the application of sleep and circadian scientific advances in cross-cutting domains.

In developing the *2011 NIH Sleep Disorders Research Plan*, the following five key goals for sleep and circadian science were identified:

*Goal 1 - Advance the understanding of sleep and circadian functions and of basic sleep and circadian mechanisms, in both the brain and the body, across the lifespan.*

*Goal 2 - Identify genetic, pathophysiological, environmental, cultural, lifestyle factors and sex and gender differences contributing to the risk of sleep and circadian disorders and disturbances, and their role in the development and pathogenesis of co-morbid diseases, and disability.*

*Goal 3 - Improve prevention, diagnosis, and treatment of sleep and circadian disorders, chronic sleep deficiency, and circadian disruption, and evaluate the resulting impact on human health.*

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<sup>1</sup> Healthy People 2020 [<http://www.healthypeople.gov/2020/>]

<sup>2</sup> Institute of Medicine. Sleep disorders and sleep deprivation: An unmet public health problem. Colten HR, Altevogt BM, editors. ISBN:0-309-66012-2, 1–500. 2006. Washington, D.C., National Academies Press.

*Goal 4 - Enhance the translation and dissemination of sleep and circadian research findings and concepts to improve health care, inform public policy, and increase community awareness to enhance human health.*

*Goal 5 - Enable sleep and circadian research training to inform science in cross-cutting domains, accelerate the pace of discovery and the translation of enhanced therapies from bench to bedside to community.*

For each of the five goals, multiple objectives have been identified and specific opportunities for scientific advances are listed. Several themes cut across multiple research goals and objectives, such as the need to understand interactions between sleep and circadian systems, the need to characterize the influence of genetic, epigenetic, and environmental factors on sleep and circadian function, and the need to conduct comparative effectiveness trials to improve and personalize treatments for sleep and circadian disorders.

In all goals and objectives, the plan recommends that consideration be given to age, sex and gender, ethnic and socio-economic differences in the burden of disease, its presentation and the clinical consequences. Special consideration is also needed to investigate the contribution of developmental processes during discrete stages of life, from perinatal development through adolescence, adulthood and aging. These research priorities are not an exhaustive list of research areas important to sleep health; therefore other innovative or significant research areas should also be considered.

As the *2011 NIH Sleep Disorders Research Plan* evolved, it was recognized that the current workforce of appropriately trained researchers is not adequate to address future research priorities. Research challenges include the need for interdisciplinary collaborations to better understand the epidemiological risks of sleep disorders and chronic sleep deficiency (Goals 2 and 3), determine the efficacy of sleep disorder interventions on health and disease risks (Goals 3 and 4), and assess comparative effectiveness of sleep disorder treatments.

## Introduction

Sleep and circadian rhythm disorders and disturbances afflict millions of Americans across all demographic groups. Three general categories of sleep and circadian disorders and disturbances have been identified: 1) disorders of sleep and circadian rhythms, 2) sleep deficiency, and 3) circadian disruption. More than ninety sleep and circadian disorders have been described in nosological systems, such as the International Classification of Sleep Disorders, 2<sup>nd</sup> edition,<sup>3</sup> and the Diagnostic and Statistical Manual of Mental Disorders<sup>4</sup>, many of which are highly prevalent:

- An estimated 50 to 70 million Americans chronically suffer from a sleep or circadian disorder.<sup>2</sup>
- Sleep-disordered breathing, including obstructive sleep apnea, affects more than 15% of the population, and causes daytime sleepiness and associated injuries (e.g., falling asleep while driving), hypertension, cognitive impairment, and is associated with metabolic syndrome, and an increased risk of heart attack, stroke and mortality<sup>2</sup>. In children, sleep-disordered breathing is associated with cardiovascular and metabolic risk factors, attention-related behavioral problems, and poor academic performance.
- Restless legs syndrome affects over one out of twenty adults, and causes difficulty sleeping and subsequent daytime sleepiness.
- Chronic insomnia affects nearly one out of five adults, and is a risk factor for depression, substance abuse, and impaired waking function; co-morbid physical (e.g., cardiopulmonary, chronic pain) and mental (e.g., depression) illnesses may be exacerbated by insomnia.
- REM sleep behavior disorder may affect one out of 250 adults and may cause patients to injure themselves or others while asleep. Recent findings associate this disorder with an increased risk of Parkinson's disease and other neurodegenerative conditions.
- Narcolepsy/cataplexy and other forms of hypersomnia affect about one in 2000 people disturbing sleep and producing excessive daytime sleepiness that profoundly reduces and quality of life and performance at work and in school.
- Chronic circadian disruptions and disorders, such as shift work syndrome and delayed sleep phase disorder, engender significant safety, health and well-being problems, including increased risk of cardiovascular disease, cerebrovascular disease, breast cancer, colorectal cancer, prostate cancer, obesity, diabetes, gastrointestinal disease, motor vehicle crashes, and difficulty adhering to school and work schedules. While population prevalence estimates of specific circadian disruptions and disorders are generally not available, an estimated 20% of the U.S. workforce is exposed to shift-work schedules.

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<sup>3</sup>The International Classification of Sleep Disorders; Diagnostic and Coding Manual. Second Edition ed. Westchester, IL: American Academy of Sleep Medicine, 2005.

<sup>4</sup>American Psychiatric Association. (2000). Diagnostic and statistical manual of mental disorders (4th ed., text revision). Washington, DC.

In addition to clinically defined disorders, chronic sleep deficiency and circadian disruption is an emerging characteristic of modern urban lifestyles and is associated with increase disease risk through multiple complex pathways in all age groups. Developing a mechanistic understanding of the threat posed by sleep deficiency and circadian disturbance to health, healthy equity, and health disparities is an urgent challenge for biomedical research in many domains. Population-based data on the prevalence of circadian disruption and its relationship to disease risk is relatively limited. However, recent findings from large multi-site cohort studies and nationally representative surveillance data from the Centers for Disease Control indicate that sleep deficiency among Americans is pervasive, and much higher than inferred from clinical data. For example:

- Nearly 70% of high school adolescents sleep less than the recommended 8-9 hours of sleep on school nights despite a physiological need. Short sleep in this age group is associated with suicide risk, obesity, depression and mood problems, low grades, and delinquent behavior.<sup>5,6</sup>
- Nationwide, 70% of adults report that they obtain insufficient sleep or rest at least once each month, and 11% report insufficient sleep or rest every day of the month.<sup>7</sup>
- Frequent sleep problems are reported by 65% of Americans including difficulty falling asleep, waking during the night, and waking feeling unrefreshed at least a few times each week, with nearly half (44%) of those saying they experience that sleep problem almost every night.<sup>8</sup>
- Short and long sleep duration is associated with up to a 2 fold increased risk of obesity, diabetes, hypertension, incident cardiovascular disease, stroke, depression, substance abuse, and all-cause mortality in multiple studies.
- Drowsy driving may be a factor in 20% of all serious motor vehicle crash injuries.<sup>2</sup> A large naturalistic study of 100 drivers and nearly 2 million miles of driving identified sleepiness as a factor in 22% of crashes, and 16% of near-crashes.<sup>9</sup> A

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<sup>5</sup> National Sleep Foundation, 2006 Sleep in America Poll, Washington, D.C.

[<http://www.sleepfoundation.org/article/sleep-america-polls/2006-teens-and-sleep>]

<sup>6</sup> Centers for Disease Control. Youth Risk Behavior Surveillance — United States, 2009. Morbidity and Mortality Weekly Report 59:1

<sup>7</sup> Centers for Disease Control. Perceived Insufficient Rest or Sleep Among Adults— United States, 2008. Morbidity and Mortality Weekly Report 58:1179.

<sup>8</sup> National Sleep Foundation, 2008 Sleep in America Poll, Washington, D.C.

[<http://www.sleepfoundation.org/article/sleep-america-polls/2008-sleep-performance-and-the-workplace>]

<sup>9</sup> Klauer SG, Dingus TA, Neale VL, Sudweeks JD, Ramsey DJ. The impact of driver inattention on near-crash/crash risk: an analysis using the 100-car naturalistic driving study data. HS810594, 1-192. 2006. Washington, D.C., National Highway Traffic Safety Administration; and Dingus TA, Klauer SG, Neale VL, Petersen A, Lee SE, Sudweeks J, Perez MA, Hankey J, Ramsey D, Gupta S, Bucher C, Doerzaph ZR, Jermeland J, Knippling RR. The 100-car naturalistic driving study; Phase II –Results of the 100-car field experiment. DOT HS 810 593, 1-352. 2006. Washington, D.C., National Highway Traffic Safety Administration.

third of Americans report falling asleep while driving 1 to 2 times per month and 26% drive drowsy during the workday.<sup>6</sup>

The high prevalence of sleep and circadian disturbances indicate an immense opportunity for research advances to reduce disease risk across the lifespan, improve on existing therapeutic approaches, and enhance public health and safety. The contribution of sleep health to living free of preventable disease, disability, injury, and premature death was recently recognized by its inclusion for the first time in Healthy People 2020, a Department of Health and Human Services initiative. Healthy People 2020 challenges communities of researchers to provide the evidence and knowledge needed to improve practices with regard to Sleep Health and over 40 other topics identified as nationwide health improvement priorities.<sup>10</sup>

Although knowledge of basic sleep and circadian mechanisms and the pathophysiology of sleep and circadian disorders and disturbances has advanced considerably since the 1996 NIH Sleep Disorders Research Plan was developed, important questions remain. For instance, studies are needed to stratify risks to health and identify vulnerable populations. Mechanistic studies are needed to define the genomic, physiological, neurobiological, and developmental impact of sleep and circadian disturbances. Recent findings indicate that sleep and circadian rhythms are coupled to chromatin remodeling and regulate as much as 20% of gene expression in peripheral tissues including the heart, liver, pancreatic islets, adipose, and immune system. Genome-wide association studies have implicated pancreatic melatonin receptor polymorphism in both blood glucose regulation and diabetes risk. Advances in basic sleep and circadian knowledge are poised to provide an improved foundation for understanding how sleep and circadian rhythms contribute to health, and why a wide range of health, performance and safety problems emerge when sleep and circadian rhythms are disrupted. Research is also needed to enhance the translation of sleep and circadian scientific advances to clinical practice, researchers in cross-cutting domains, and communities. An independent systematic review of evidence organized by the National Institute of Mental Health and the Office of Medical Applications of Research on manifestations and management of insomnia concluded that there is an urgent need to improve the evidence base guiding clinical practice in terms of treatment efficacy and comparative effectiveness.<sup>11</sup>

In developing this *2011 NIH Sleep Disorders Research Plan*, five key goals were identified by the Sleep Disorders Research Advisory Board based upon input from the public<sup>12</sup>; patients with sleep and circadian disorders; relevant patient organizations; members of the scientific community studying sleep and circadian rhythms and related

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<sup>10</sup> Healthy People 2020. ODPHP Publication No. B0132. Department of Health and Human Services, 2010.

<sup>11</sup> NIH State-of-the-Science Conference Statement on Manifestations and Management of Chronic Insomnia in Adults. NIH Consens Sci Statements. 2005. Jun 13-15; 22(2) 1–30.

<sup>12</sup> Request for Information (RFI): Sleep Disorders Research Plan (NOT-HL-11-107), NIH Guide June 9, 2010.



disorders; clinicians treating patients with sleep and circadian disorders; relevant professional societies; and the Trans-NIH Sleep Research Coordinating Committee to provide guidance for sleep and circadian science initiatives in the near future. These goals were identified as exceptional opportunities for sleep and circadian research during the next 3 to 5 years.

*Goal 1 - Advance the understanding of sleep and circadian functions and of basic sleep and circadian mechanisms, in both the brain and the body, across the lifespan.*

*Goal 2 - Identify genetic, pathophysiological, environmental, cultural, lifestyle factors, age, and sex and gender differences contributing to the risk of sleep and circadian disorders and disturbances, and their role in the development and pathogenesis of co-morbid diseases, and disability.*

*Goal 3 - Improve prevention, diagnosis, and treatment of sleep and circadian disorders, chronic sleep deficiency, and circadian disruption, and evaluate the resulting impact on human health.*

*Goal 4 - Enhance the translation and dissemination of sleep and circadian research findings and concepts to improve health care, inform public policy, and increase community awareness to enhance human health.*

*Goal 5 - Enable sleep and circadian research training to inform science in cross-cutting domains, accelerate the pace of discovery and the translation of enhanced therapies from bench to bedside to community.*

For Goals 1-4, high-priority objectives are identified with examples of potential opportunities for scientific advance. The goals and objectives encompass cross-cutting themes and research approaches including the interactions between sleep and circadian systems, genetic and epigenetic studies that may inform personalized medicine, the role of environment and gene-environment interaction in the development of sleep and circadian disorders, and opportunities for comparative effectiveness research. Integrative research approaches present additional opportunities to leverage efforts in more than one goal area.

Goal 5 acknowledges the role of individuals developing research skills and knowledge dissemination as critical steps toward accomplishing the scientific goals and opportunities included in this plan. Sleep deficiency and circadian disorders and disturbances are associated with many pathophysiological conditions presenting diverse opportunities for scientific cross-fertilization and skill development. The strength of sleep and circadian science will be an important driver of future interest from researchers joining interdisciplinary collaborative teams for comprehensive studies of sleep, health, and disease linkages and the development of improved approaches for treatment and prevention.

The approach to the *2011 NIH Sleep Disorders Research Plan* was to focus attention on exceptional selected opportunities for research and potentially improving health. Scientific directions mentioned in this strategic plan are by no means an exhaustive list of research opportunities; indeed, many additional opportunities are worthy of scientific inquiry, and others may emerge unexpectedly with new findings and advances. The Plan is the starting point for a "living" document and ongoing discussion with the Advisory Board and research communities. Researchers should take into consideration scientific advances, evidence of emerging health needs, and evolving technological capabilities that routinely define current needs and priorities.

## Goal 1

### **Advance the understanding of sleep and circadian functions and of basic sleep and circadian mechanisms, in both the brain and the body, across the lifespan.**

Research in the basic science of sleep and circadian rhythms provides a foundation for understanding how these regulatory processes and functions contribute to health, and why a wide range of health and day-to-day performance deficits emerge when sleep or circadian rhythms are disturbed. The understanding of the basic biochemical, physiological and neural mechanisms that underlie regulation of sleep and circadian rhythms has advanced rapidly over the last several decades. These advances open new opportunities to characterize further the basic principles of how sleep and circadian rhythms are regulated, and uncover the mechanisms underlying the known and hypothetical functions of sleep or circadian rhythmicity. In this regard, studies are needed to improve our understanding of how homeostatic and circadian mechanisms regulate sleep, the ways that different circadian clocks in the body are coordinated, and the role of sleep and circadian rhythms in modifying brain and body functions.

There is an immediate opportunity to improve our understanding of the varied consequences associated with sleep deficiency and circadian disruption through studies at the basic and molecular science levels. Cellular mechanisms at the forefront of pathophysiological analysis are affected by sleep deficiency including unfolded protein responses and various forms of epigenetic modification. Acute and chronic sleep restriction or fragmentation are commonly experienced by individuals and associated with impaired learning, neurobehavioral function, affective behavior, and memory functions. Studies are needed to elucidate the neurobiological pathophysiology caused by sleep deficiency and its neurological consequences. Sleep and circadian disturbances are also associated with a diverse array of pathophysiological conditions and disease risks such as insulin resistance, diabetes, cardiovascular disease, stroke, and cancer. New approaches are needed to systematically study the specific contributions of sleep and circadian disruption since alterations of sleep also have circadian consequences. Elucidating the mechanisms of sleep-circadian interactions will have broad fundamental implications for future studies of physiology and disease risk.

Despite the evolutionary development of sleep physiology in relationship to regular day-night cycles, a wide range of individual variation exists in sleep phenotypes and tolerance to sleep deficiency or circadian disruption. The determinants of this variation include genetic differences in sleep or circadian regulation, environmental and social factors (artificial light exposure, job requirements, parental responsibilities, social interactions, sleep environment, etc.), developmental/aging factors, sex and gender, ethnicity, socio-economic status, diet, certain neurological conditions, and other diseases. Improving our understanding of the basis for individual differences in sleep and circadian timing will open an array of new opportunities for translation, improved therapies for co-morbid conditions, and the development of coupled health promotion strategies.

Within the scope of the overarching Goal 1, examples of research objectives identified as potentially high impact over the next five years include the following:

### **Objective 1**

***Elucidate genetic, epigenetic and environmental mechanisms underlying individual differences in wake-sleep and circadian regulation and contributing to differences in vulnerability to sleep deficiency and circadian disturbances.***

#### **Examples of Scientific Opportunity:**

- Identify genomic, proteomic, metabolic, and developmental biomarkers of sleep deficiency and biological timing enabling objective assessments of the associated health risks.
- Identify sleep or circadian genotypes and phenotypes that predispose to, or protect against, the consequences of sleep deficiency and circadian disturbance in various functional domains such as neurobehavioral function, metabolic regulation, and cardiopulmonary pathophysiology.
- Identify environmental factors that modify vulnerability or protect against cognitive, metabolic, cardiovascular and other functional impairment associated with sleep deficiency and circadian disruption.

### **Objective 2**

***Elucidate mechanisms of sleep deficiency and circadian disruption contributing to the erosion of metabolic, immune, inflammatory, neurologic, psychiatric and cardiopulmonary function across the lifespan.***

#### **Examples of Scientific Opportunity:**

- Differentiate the consequences of sleep deficiency (due to acute sleep loss, chronic sleep loss or chronic sleep disruption) and circadian disruption with respect to known disease pathways such as disordered glucose regulation, inflammation, vascular reactivity and metabolism.
- Elucidate neurobiological mechanisms coupling sleep deficiency (due to acute sleep loss, chronic insufficient sleep or chronic sleep disruption) and chronic circadian disruption to the etiology of mental, attention, anxiety, stress, pain, and depressive disorders, and as a modifier of treatment outcomes.
- Elucidate the role of sleep and circadian disturbances and disorders in the pathophysiology of immune and inflammatory disorders, neurological autoimmune attacks, fatigue, and renal failure.
- Elucidate the effects of sleep deficiency caused by sleep-disordered breathing on upper airway function and respiratory regulation.

### **Objective 3**

***Improve our understanding of the neural processes involved in wake-sleep and circadian control, especially those associated with homeostatic sleep pressure, wake-sleep state transitions and interaction with circadian control mechanisms.***

#### **Examples of Scientific Opportunity:**

- Identify neurological, anatomical, biochemical, and genomic substrates of homeostatic sleep pressure and the physiological mechanisms of sleep pressure build-up and dissipation.
- Identify the mechanisms by which homeostatic sleep pressure acts on endogenous wake-sleep circuits, determine how this occurs during acute vs. chronic sleep disruption, and how these processes are altered in primary sleep disorders such as narcolepsy and other hypersomnias, as well as insomnias.
- Elucidate neurobiological processes switching the brain between wake, rapid eye movement (REM) sleep and non-REM states, pathways responsible for coordinating wake-sleep with circadian rhythms, and the abnormalities associated with motor system disorders such as the restless legs syndrome, periodic limb movement disorder, cataplexy and REM sleep behavior disorder.

#### **Objective 4**

***Elucidate the pathophysiological consequences of sleep deficiency on synaptic neuroplasticity, learning, and memory.***

#### **Example of Scientific Opportunity:**

- Elucidate molecular pathophysiological mechanisms and windows of vulnerability to sleep deficiency and circadian disruption with respect to impaired neurological development and function, maintenance of synaptic function across the lifespan, and disorders of aging.
- Elucidate the impact of sleep deficiency on adaptive versus maladaptive neuroplasticity during repair and regeneration.

#### **Objective 5**

***Elucidate organismal, tissue and cellular levels of physiological organization that are affected by circadian disruption, the role in disease risk and as a modifier of therapeutic response.***

#### **Example of Scientific Opportunity:**

- Elucidate neurobiological and other pathways coupling circadian rhythms to disease pathophysiology (e.g., abnormal secretion of insulin by the pancreas), environmental exposures (e.g. diet), and the chronobiology of pharmacotherapeutic responses.

## **Goal 2**

**Identify genetic, pathophysiological, environmental, cultural, lifestyle factors and sex and gender differences contributing to the risk of sleep and circadian disorders and disturbances, and their role in the development and pathogenesis of co-morbid diseases, and disability.**

Sleep and circadian disorders research is well-poised to capitalize on the scientific momentum of recent years. Genetic risk factors have been discovered for narcolepsy, restless leg syndrome and circadian phase disorders. Progress has been made defining etiological pathways such as iron and the production of dopamine in restless leg syndrome; autoimmune destruction of hypocretin cells in narcolepsy; and compromised anatomy, increased collapsibility, disturbed muscle control of the upper airway, and loop gain abnormalities in respiratory control in sleep-disordered breathing. Starting from these advances, there are new opportunities to follow-through on the discovery process with translation and therapeutic development. A core avenue for investigation is understanding how sleep deficiency translates at the molecular level into brain and organ pathophysiology. Many sleep and circadian disorders are clearly multifactorial or heterogeneous in etiology. Studies are needed to identify clinically meaningful subtypes, and algorithms informing the selection of optimal therapeutic strategies. Physiological assessments, next generation sequencing, integrative genomics, epigenetics, computational modeling, and other approaches are available to define clustered disease signatures and assess the impact of a sleep disorder or individual risk. Identifying genomic profiles for subsets of patients with sleep apnea, insomnia, hypersomnia, delayed sleep phase disorder or restless leg syndrome, will open new avenues for research that will define the clinical and etiological significance of disorder differences. Chronic pharmacotherapies for sleep disorders need study to prevent exacerbation or loss of efficacy over time. Signatures for disease stratification will make comparative outcome studies more informative and enhance the accuracy of disease outcome predictions. Molecular signatures for sleep deficiency and disorders are also urgently needed to facilitate the identification of emerging pharmacotherapies that aim to accelerate, delay, dampen, or amplify selected molecular mechanisms regulating the circadian periodicity of individual cells and tissues.

In many instances, sleep and circadian disorders are the result of complex gene-environment interactions. For example, lack of exercise and unhealthy food habits are likely to predispose to sleep apnea more in patients with specific craniofacial features (e.g., micrognathia) or specific genes. Similarly, the circadian disruption associated with shift work may potentiate the adverse impact of sleep-disordered breathing on metabolic disturbances in obesity or on the development of cardiovascular disease. Race and ethnicity is emerging as a risk factor for sleep apnea independent of obesity, and the tolerance and physiological impact of shift work may vary as a function of genetic factors. Gene-environment interactions pose special challenges and mandate the study of environmental factors in conjunction with genetic or structural predisposing factors. Environmental effects are especially important in the context of prevention, as it may be possible to act to reduce disease burden.

Maintaining the overall momentum of sleep and circadian disorders research requires continued development of model organisms for hypothesis testing at the forefront of understanding. While an assortment of animal models ranging from fruit fly and zebra fish to transgenic and knockout mice is available, significant gaps remain a barrier to research. For instance, animal models are needed where the long-term effects of repetitive upper airway occlusion on cardiovascular pathophysiology can be studied directly. Additionally, there is no animal model for REM sleep behavior disorder or for

restless legs syndrome. Transgenic animal models are also needed to improve our understanding of human polymorphisms in clock related genes change cellular function, and metabolic susceptibility to circadian disruption.

Research is needed to explore sleep or circadian disturbances and disorders as potentially modifiable risk factors for various negative health outcomes of co-morbid conditions and determining survivorship (such as hypertension/cardiovascular disease, obesity, diabetes, mental disorders, cancer, neurodevelopmental disorders). Sleep disorders may also serve as an intermediate marker on which to stratify co-morbid disease risk. For example, insomnia is associated with the development of depression in longitudinal studies, but it is not known whether differences in neurobiology exist where insomnia is associated with depression versus cases involving insomnia alone. Chronic sleep deficiency and circadian disruption are common during childhood and may predispose to future mental health problems, such as depression, attention deficits, hyperactivity, impulsivity, alcohol and substance abuse, and even suicide. Circadian disruption, sleep deficiency and sleep and circadian disorders and disturbances may also predict the pathophysiology or progression of certain cancers or the response to cancer therapy. Yet, the molecular mechanisms connecting circadian clock genes with cell cycle genes and potential abnormalities leading to the cancer phenotype remain challenges for future research.

Sleep researchers are poised to make significant advances elucidating the neurobiology mediating the effects of sleep deficiency and circadian disruption on behavior regulating brain regions during childhood, and during the aging process.

### **Objective 1**

***Discover molecular, cellular, genetic, epigenetic and systems-level factors involved in predisposition, cause, or modified disease course (severity, prognosis) of sleep and circadian disorders.***

#### **Examples of Scientific Opportunity:**

- Identify mutations/polymorphisms in specific genes causing sleep or circadian disorders (e.g., mutations in familial cases of restless leg syndrome or advanced sleep phase disorder, or mutations predisposing to sleep deficiency or affecting vulnerability to sleep loss or circadian disruption).
- Enable better diagnosis, prevention, and treatment of sleep disorders by identifying genetic, biochemical, and other markers that characterize sub-types of sleep and circadian disorders.

### **Objective 2**

***Identify interactions between genes, endophenotypes and environment including sex and gender differences, ethnic, socio-economic, cultural and lifestyle factors associated with predisposition to, or modified disease course (developmental course, severity, prognosis, disability) of sleep and circadian disorders.***

#### **Examples of Scientific Opportunity:**

- Identify the contribution of sleep apnea to cardiovascular disease in the presence or absence of other risk factors (e.g., diabetes, obesity and genetics) and the contribution of sex and gender differences, socio-economic, cultural, ethnic, and lifestyle factors.
- Elucidate genetic risk factors and the role of environment in conditions such as shift work disorder, narcolepsy, restless leg syndrome and other sleep and circadian disorders.

### **Objective 3**

***Identify the processes by which sleep and circadian disturbances or disorders during vulnerable periods of development confer risk in the trajectory of normal brain development and associated peripheral systems as well as differential impact by age, sex and gender, socio-economic and ethnic background.***

#### **Examples of Scientific Opportunity:**

- Determine whether and how chronic sleep deficiency or circadian disruption (e.g., delayed sleep phase disorder) during childhood and adolescence impact brain development or circuitry and predispose to affective, attention and impulse control disorders and health (e.g., development of autonomic nervous system regulation, energy metabolism).
- Assess which demographic, cultural, sex and gender, socio-economic and lifestyle factors interact with sleep and circadian disruption in childhood and adolescence to increase risk of physical or mental health disorders.
- Elucidate the risk of sleep disorders due to neurodevelopmental abnormalities.

### **Objective 4**

***Identify and validate novel model systems to facilitate understanding of the mechanisms underlying sleep and circadian disorders and the mechanisms by which sleep and circadian disorders may impact health and predispose to diseases.***

#### **Example of Scientific Opportunity:**

- Develop animal models of sleep and circadian disturbances and disorders that have been validated for relevance to corresponding human conditions.
- Determine the relationship between circadian phase at the organismal, tissue or cellular levels with standard measures of cognitive, emotional and physical health.
- Determine how resetting the phase, enhancing the amplitude or altering the period of the circadian clock at the organismal, tissue or cellular levels could lead to new treatment approaches for diseases that involve or are affected by circadian disruption.
- Identify the relationship between circadian timing mechanisms and outcomes of medical procedures, such as organ transplantation, gastric bypass surgery, cancer chemotherapy and immunotherapy, as well as medical management with prescription drugs.



***Objective 5: Determine whether sleep and circadian disorders or disturbances predispose or contribute to cardiovascular, metabolic, cancer, mental or other disorders, and determine if novel sleep- and circadian-related treatment approaches can significantly modify the development or progression of those conditions.***

**Examples of Scientific Opportunity:**

- Identify strategies that lead to long-term behavioral changes, such as increased sleep duration, improved continuous positive airway pressure (CPAP) adherence, or circadian realignment, and measure the effects of such interventions on disease or health outcomes.
- Determine if treatment of sleep and circadian disturbances and disorders (e.g., shift work disorder, delayed sleep phase disorder) alter associated morbidity or disease progression in high impact diseases such as cardiovascular, renal, metabolic, mental, or neoplastic disorders.
- Examine the role of sleep and circadian disorders in the development and progression of central nervous system disorders such as neurodegenerative disorders, substance abuse, and neurodevelopmental disorders.

**Goal 3**

**Improve prevention, diagnosis, and treatment of sleep and circadian disorders, chronic sleep deficiency, and circadian disruption, and evaluate the resulting impact on human health.**

Despite advances in the recognition and description of sleep and circadian disorders and disturbances, little progress in prevention, access to care and personalized treatment has been made. Research is needed to develop prevention strategies, to find more available and cost effective diagnostic techniques, to discover novel and personalized treatments and to improve existing treatments. Estimates suggest that a majority of individuals with sleep and circadian disorders are undiagnosed and inadequately treated. Moreover, access to care is limited because management of sleep and circadian disorders often involves specialized training and/or a costly, time-consuming diagnostic evaluation (i.e., polysomnography). There is an unmet need for novel, personalized and cost-effective methods to prevent, diagnose, and treat individuals with sleep and circadian disorders. Current knowledge presents scientific opportunities for such advances. For example, a number of genes are associated with restless legs syndrome, circadian disorders, and narcolepsy. Further research to determine the functional relationship of the gene variants associated with these diseases may lead to improved diagnosis and treatment. In addition, if new assessment technologies and treatment pathways available for sleep-disordered breathing are demonstrated to result in positive health outcomes, such advances may significantly improve access to care. Exceptional opportunities exist for bioengineering research to enhance the evaluation, diagnosis, and treatment of sleep and circadian disorders. For example, technological enhancement of continuous positive airway pressure (CPAP) devices may allow the stratification of sleep apnea patients into populations with and

without a collapsible airway. Advances in polysomnographic interpretation and technology may reveal a biomarker of insomnia that predicts depression, or a polysomnographic measure of REM sleep behavior disorder that predicts the development of Lewy body disease. Similarly, technological capabilities allowing the airway to be imaged in real time during the night while recording sleep, or image hypocretin cells *in vivo* through a brain scan, would significantly enhance sleep disorders medicine.

Even among individuals whose sleep symptoms are not severe enough to merit diagnosis of a sleep or circadian disorder, sleep and circadian disturbances marked by chronic sleep deficiency or circadian disruption are very common, in both children and adults. These subclinical conditions often impact physiological and behavioral processes relevant to health and safety. Epidemiology and laboratory investigations provide clear associations of sleep deficiency with obesity, diabetes, cardiovascular disease, mood, behavior, addictive behaviors such as drug and alcohol use and abuse, and mortality. However, insufficient knowledge exists to explain the biochemical or physiological changes that underlie the increased risk for such morbidities. Little is known about who might be particularly susceptible to those risks or about behavioral interventions that might mitigate the risk. Similarly, circadian disruption may contribute to disease even when sleep duration appears adequate. New methodologies are needed to diagnose circadian disruption and to synchronize circadian timing in cells, tissues, and the whole organism to positively influence health. Finally, there is increasing evidence that sleep and circadian disorders, chronic sleep deficiency and circadian disruption can each evolve dynamically with development, differ substantially at different points across the lifespan from infancy to old age, and vary considerably between the sexes. Research on sleep and circadian disturbances and disorders is likely to have greatest impact when it can differentiate between prevention, diagnostic, and therapeutic strategies that take development, age and sex and gender into account.

Thus, the objectives to make scientific advances directed toward Goal 3 are threefold:

#### ***Objective 1***

***Develop optimal strategies for the prevention, diagnosis and therapy of sleep and circadian disorders, during development and with respect to the needs of specific co-morbid diseases (e.g., cardiovascular disease, cerebrovascular disease, epilepsy, depression, addiction).***

#### **Examples of Scientific Opportunity:**

- Compare the impact of existing therapeutic strategies for sleep and circadian disorders on adherence, health outcomes and cost effectiveness.
- Identify biomarkers of sleep and circadian disorders that will facilitate personalized treatments, and clarify the risk associated with untreated sleep and circadian disorders and disturbances.

#### ***Objective 2***

***Evaluate novel prevention and intervention approaches for chronic sleep deficiency and associated diseases, and assess their impact on health during***

***different stages of development, across the lifespan, and for each sex and gender.***

**Examples of Scientific Opportunity:**

- Determine whether increasing sleep duration reduces the negative cognitive, emotional, cardiovascular and metabolic impact associated with habitual sleep deficiency.
- Assess and compare efficacy and effectiveness of treating chronic sleep deficiency alone and in combination with interventions to reduce circadian disruption on disease (e.g. depression, pain, cancer, metabolic syndrome) and disease progression.
- Assess and compare efficacy and effectiveness of lifestyle or behavioral interventions to decrease the negative effects of chronic sleep deficiency in different demographic, ethnic and socio-economic groups.

**Objective 3**

***Evaluate the efficacy and health impact—during development, across the lifespan, and for each sex and gender—of novel prevention and interventional approaches for circadian disruption and disorders, and for diseases associated with those conditions.***

**Examples of Scientific Opportunity:**

- Assess the efficacy of interventions to improve circadian phase alignment, amplitude, or period of the circadian clock on disorders influenced by circadian disruption.
- Assess and compare the efficacy of circadian-coupled interventions (chronomedicine) on the outcome of medical procedures (e.g. organ transplantation, gastric bypass surgery, cancer chemotherapy, immunotherapy), and the medical management of chronic conditions (e.g. hypertension, diabetes, hyperlipidemia, vascular disease, and thrombosis) with prescription drugs.
- Assess the impact of novel interventions to optimize sleep duration and circadian alignment in order to prevent unhealthy outcomes such as obesity, accidents, work-related injuries, cognitive impairments and behavioral and mood dysregulation.

**Goal 4**

**Enhance the translation and dissemination of sleep and circadian research findings and concepts to improve health care, inform public policy, and increase community awareness to enhance human health**

The translation and dissemination of basic and clinical sleep and circadian rhythm research findings have the potential to dramatically improve public health and safety. For instance, translation of sleep and circadian rhythm research findings could help stem the rising tide of obesity and associated metabolic disorders, provide new avenues in the prevention and treatment of cardiovascular disease and mental health disorders,

improve the health and quality of life for those with sleep and circadian disturbances and disorders, and improve the safety, health and productivity of workers, particularly in the transportation and medical professions. However, among health care professionals, educators, policy makers and the general public, there is widespread lack of awareness of the importance of sleep and circadian regulation for physical and mental health and safety. There is a need to develop and evaluate specific approaches and methods for translation of sleep and circadian rhythm research findings.

Public awareness of the benefits of adequate sleep and optimal circadian regulation on health and the hazards of sleep deficiency and circadian disruption can be enhanced through educational research. Qualitative and public health research strategies can be employed to develop effective messages and information that could change attitudes, beliefs and values about the risks associated with sleep deficiency and circadian disruption, and the importance of adequate sleep and optimal circadian regulation to physical and mental health. Research to develop such strategies is needed in diverse populations of all ages, with considerations for ethnic, socio-economic and sex and gender differences, and in specific populations (e.g., shift workers, physicians, nurses, police officers, transportation workers, students, families and communities). Research is also needed to develop health strategies addressing societal, sociological, and psychosocial factors in conflict with optimal sleep and circadian outcomes. However, in order for such efforts to be successful in improving healthy sleep behavior, they must build on consistent and convincing findings from laboratory and clinical research. For instance, influencing public attitudes depends in part on the availability of evidence-based recommendations on the amount of sleep needed to avoid adverse health outcomes, motor vehicle crashes, occupational errors and accidents, cognitive and learning impairments, and other relevant outcomes. Research that addresses these fundamental questions has the potential to hasten translation, inform public policy, and enhance human health and safety.

Even with access to primary healthcare, a majority of those with sleep and circadian disturbances and disorders are undiagnosed or misdiagnosed and remain untreated. Little is known regarding the barriers and facilitators to the identification and treatment of sleep and circadian disturbances and disorders in primary or specialty care settings or of the delivery models that most effectively address these conditions. Likewise, for those who are diagnosed with a sleep or circadian disorder, it is not known what information or approaches best promote adherence to treatments. To support this translation, more information is needed regarding the effects of treatment and treatment adherence on quality of life and health outcomes for a range of sleep and circadian disturbances and disorders.

Sleep and circadian disturbances and disorders play an important role in human health and safety. In occupations where 24-hour operations are routine, the evidence of increased risk of disease and safety hazards is well known. For instance, concerns about patient safety in U.S. hospitals led the Institute of Medicine to recommend elimination of nursing shifts longer than 12 hours in its 2004 report entitled *Keeping*

*Patients Safe: Transforming the Work Environment of Nurses.*<sup>13</sup> In 2009, the Institute of Medicine concluded in *Resident Duty Hours: Enhancing Sleep, Supervision, and Safety*, that it is hazardous for resident physicians to work for more than 16 consecutive hours without sleep.<sup>14</sup> As of 2011, an estimated 84,000 resident physicians in post-graduate year two and beyond will continue to work 28 consecutive hour shifts until research ascertains the risks associated with extended duration shifts in these more experienced resident physicians.

While the need for increased knowledge of the risks associated with sleep deficiency is an important element, studies are also needed to assess the efficacy of optimizing sleep health with respect to biomedical, safety, and performance outcomes. Translational research will also be needed to assess the effectiveness of strategies promoting the alignment of sleep need with real world schedules and behavioral factors. Validated sleep and circadian interventions will facilitate the consideration of sleep and circadian rhythm knowledge by individuals, employers, health care providers, and potentially future health policy.

### ***Objective 1***

***Facilitate translation of sleep- and circadian-based interventions to diverse populations and settings.***

#### **Examples of Scientific Opportunity:**

- Identify barriers to the implementation of screening, evaluation and treatment of primary and co-morbid sleep and circadian disorders in primary care, mental health and specialty care settings.
- Identify educational content and strategies that effectively motivate individuals with untreated sleep and circadian disorders and disturbances to seek and adhere to evidenced-based treatments and evaluate the impact on quality of life, morbidity, and mortality.
- Enhance education strategies for both clinicians and patients to improve communication about sleep issues in relation to health and quality of life.

### **Goal 5**

**Enable sleep and circadian research training to inform science in cross-cutting domains, accelerate the pace of discovery, and the translation of enhanced therapies from bench to bedside to community.**

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<sup>13</sup> Institute of Medicine of the National Academies. *Keeping Patients Safe: Transforming the Work Environment of Nurses*. 2004. Washington, D.C., The National Academies Press.

<sup>14</sup> Institute of Medicine of the National Academies. *Resident Duty Hours: Enhancing Sleep, Supervision, and Safety*. Ulmer C, Wolman DM, Johns MME, editors. 1–322. 2008. Washington, D.C., The National Academies Press.

An ongoing challenge for sleep and circadian research is the limited pipeline of investigators. New directions for sleep and circadian research have rapidly expanded over the last decade to encompass many domains of biological investigation, experimental approaches, and state-of-the-art technologies. The capacity to sustain the pace of discovery in sleep and circadian research reflects, in part, on the strength of the scientific opportunity, the potential to substantially impact medicine, and the commitment of a supportive community of investigators at the forefront of recruitment and mentoring. The scale and complexity of today's sleep and circadian research opportunities demand that investigators acquire new capabilities outside the confines of a single discipline and explore new organizational models for research.

In addressing training needs, many opportunities to attract future researchers into the career pipeline may be open for consideration including high school, undergraduate school, graduate and medical school, postdoctoral fellowship, early career development and mid-career retraining. For instance, a widely disseminated curriculum supplement developed by the NIH Office of Science Education and NHLBI aims to stimulate the interest of high school students in sleep and biological rhythms. The importance of one-on-one mentoring increases with higher levels of education through early career development. NIH supported competitive funding mechanisms are available to protect the time of research faculty for mentoring activities and enhance the career and skill development of trainees, early stage investigators, and mid-career professionals.

Thus, objectives for this goal include the following:

### **Objective 1**

**Attract individuals to careers in sleep and circadian research at all levels.**

#### **Examples of Potential Training Opportunity:**

- Incorporate appropriate sleep and circadian concepts in undergraduate, graduate and postgraduate curricula.
- Promote opportunities for knowledge application and collaboration by enhancing the awareness of sleep and circadian concepts among academic investigators in cross-cutting scientific disciplines.
- Provide access to information to help undergraduates consider and find positions for post-graduate degrees (e.g. Ph.D., M.D. Ph.D.) in sleep and circadian science.

### **Objective 2**

**Assess, report, and increase awareness of the NIH mechanisms available to support institutional and individual training in sleep and circadian research.**

#### **Examples of Potential Training Opportunity:**

- Identify specific segments of research training which may be suboptimal or present opportunities to address scientific needs.
- Communicate opportunities to enhance research.

## Appendix 1 – Glossary

Following is a glossary of some of the terms commonly used in this strategic plan. More complete definitions of clinical disorders are available in the nosologies produced by relevant societies.<sup>3,4</sup> As there is increasing evidence that sub-clinical conditions, such as chronic insufficient sleep or recurrent shifting of circadian phase, may have adverse health effects, it was necessary to develop consistent terminology to refer to such conditions. As described below, the terms disruption, disturbance and disorder have been used to represent a continuum of chronicity and presumed clinical impact. Dysregulation indicates impairment of a regulatory mechanism, and sleep deficiency occurs whenever the amount or quality of sleep obtained is less than is needed.

**Atonia of Postural Muscles:** Muscle that has lost its strength (paralysis). Atonia is a normal characteristic of the rapid eye movement (REM) stage of sleep and the most vivid periods of dreaming. If the loss of muscle tone is insufficient during the REM sleep stage, mild limb twitches or vigorous movements can occur (rapid eye movement behavior disorder). In narcolepsy, episodes of muscle weakness while awake can affect posture, slur speech, impair vision, and in some cases produce total collapse.

**Advanced sleep phase disorder:** Advanced sleep phase disorder is characterized by habitual sleep onset and wake-up times that are several hours earlier than conventional or desired times. Affected individuals complain of sleepiness in the late afternoon or early evening, early sleep onset, and spontaneous early morning awakening.

**Cataplexy:** Brief episodes of partial or total atonia of postural muscles during wakefulness triggered by emotional experiences (e.g., laughter, surprise); cataplexy most commonly occurs as a symptom of narcolepsy

**Circadian disruption:** circadian dysregulation, alteration in circadian amplitude or misalignment of circadian phase, as occurs following the transition to daylight savings time on weekends vs. weekdays, or travel across time zones, and similar problems often collectively termed social jet lag

**Circadian disorder:** Disorders of circadian rhythms are clinical conditions resulting from intrinsic or extrinsic circadian disruption, that cause disability or dysfunction in physical and mental health, function or capacity. Circadian phase disorders can occur when the timing of our personal biological clock is out of synch with either environment or life schedule (e.g. shift work and jet lag disorder). Another type of circadian disorder can occur when “cues” (e.g. daylight, meals) helping to bring the chemistry of biological clock time into synchronization with the real world go unrecognized (e.g. non-24-hour circadian rhythm disorder).

**Circadian disturbance:** recurrent circadian disruption

**Circadian dysregulation:** impairment of the physiological regulatory mechanism that governs the circadian timing of neural and humoral functions of the brain and body

**Circadian rhythm:** physiological, behavioral, or psychological processes that fluctuate in regular and predictable cycles, with a cycle duration of approximately 24-hours

**Circadian rhythm sleep disorder:** sleep disorder caused by entrainment at an adverse (advanced or delayed) circadian phase, such as delayed sleep phase disorder, misalignment of circadian phase or circadian entrainment failure, as occurs in non-24-hour sleep-wake disorder

**Delayed sleep phase disorder:** Delayed sleep phase disorder is characterized by habitual sleep-wake times that occur intractably later than desired or required, with affected individuals complaining of difficulty falling asleep early enough to obtain an adequate amount of sleep prior to their required wake time. When affected individuals are allowed to initiate sleep at a later hour, they are often able to sleep soundly until late morning or early afternoon.

**Drowsiness:** a fluctuating intermediate state between alert wakefulness and sleep, that is most often experienced when individuals are struggling to maintain wakefulness at a time appropriate for sleep, as a result of pathologic conditions or sleep deficiency

**Homeostatic sleep pressure:** The concept that the propensity for sleep reflects a balance between the need for sleep as a function of the amount of time elapsed since the last adequate sleep episode, and circadian rhythms which determine the timing of an optimally structured and restorative sleep episode.

**Hypersomnia:** A state characterized by subjective report of tiredness and objective evidence of inability to maintain vigilance.

**Hypnagogic hallucination:** A symptom characteristic of narcolepsy in which the patient is aware of vivid imagery which appears to have the qualities of being real.

**Insomnia:** A chronic or acute sleep disorder characterized by a complaint of difficulty initiating, and/or maintaining sleep, and/or a subjective complaint of poor sleep quality that result in daytime impairment and subjective report of impairment.

**Loop gain abnormalities:** An engineering concept commonly used by researchers to describe the accuracy with which the body responds to difficulty breathing (e.g. airway obstruction associated with sleep apnea). Abnormalities in the regulation of breathing are a common characteristic of sleep apnea.

**Narcolepsy:** A disorder of sleep and wakefulness characterized by excessive daytime sleepiness, disrupted nighttime sleep, and various combinations of irresistible onset of sleep, cataplexy, hypnagogic hallucinations or sleep paralysis. Narcolepsy is thought to result from disease processes affecting brain mechanisms that regulate REM sleep.

**Non-REM sleep:** Non-REM sleep is a state of consciousness that ranges from the light dozing associated with the initial transition from wakefulness to sleep to deep sleep characterized by high-amplitude slow waves detectable in electroencephalographic recordings. Non-REM sleep constitutes most of the nightly sleep episode, though it is periodically interrupted by the occurrence of REM sleep (see below).

**Nosology:** The classification of disease by cause (etiology), the biological pathway by which the disease is caused (mechanism), or by symptom(s). A nosology can facilitate research and diagnosis by systematically organizing the symptoms and medical factors that define a particular disease or syndrome.



**Obstructive sleep apnea (OSA):** a chronic disorder characterized by inability to maintain adequate ventilation during sleep due to sleep-related increase in upper airway resistance, while breathing during wakefulness is satisfactory

**Periodic limb movement disorder (PLMD):** Periodic limb movement disorder is characterized by periodic episodes of repetitive, highly stereotyped, limb movements that occur during sleep.

**REM sleep:** Rapid eye movement sleep is one of the two major types of sleep. Episodes of REM sleep occur in approximately every 90 to 100 minutes during the night. The REM sleep episodes increase in duration through the night and are characterized by a relatively low voltage, fast frequency EEG, skeletal muscle atonia, rapid eye movements, and dreaming.

**Restless legs syndrome (RLS):** Restless legs syndrome is a sensorimotor disorder characterized by a complaint of a strong, nearly irresistible, urge to move the legs that is often made worse by rest and is partially and temporarily relieved by walking or moving the legs. The urge to move the legs worsens in the evening or night with relative relief in the morning.

**Shift work disorder (SWD):** a circadian rhythm sleep disorder characterized by insomnia during daytime sleep or excessive sleepiness during work hours scheduled during the habitual sleep period.

**Sleep ability:** the ability to fall and stay asleep, often measured at various times of day using the multiple sleep latency test or other technique.

**Sleep deficiency:** deficit in the quantity or quality of sleep obtained versus the amount needed for optimal health, performance and well being; Sleep deficiency may result from prolonged wakefulness leading to sleep deprivation, insufficient sleep duration, sleep fragmentation or a sleep disorder, such as in obstructive sleep apnea, that disrupts sleep and thereby renders sleep non-restorative.

**Sleep disorder:** sleep disorders are clinical conditions that are a consequence of a disturbance in the ability to initiate or maintain the quantity and quality of sleep needed for optimal health, performance and well being.

**Sleep-disordered breathing (SDB):** a broader category than obstructive sleep apnea in that it also includes syndromes in which breathing is disturbed during sleep as a result of sleep-related suppression of the central drive for breathing

**Sleep disruption:** dysregulation of sleep homeostasis, sleep deficiency, sleep fragmentation, insufficient sleep or impairment of sleep quality or quantity caused by a sleep disorder

**Sleep disturbance:** chronic sleep disruption

**Sleep fragmentation:** repeated interruption of sleep, generally characterized by recurring, brief episodes of wakefulness

**Sleep homeostasis:** the regulatory process governing sleep duration and intensity in response to wakefulness, such that increases in sleep intensity and duration follow prolonged wakefulness or disrupted sleep

**Sleep hygiene:** the practice of controlling behavioral and environmental factors that may interfere with sleep in an attempt to improve sleep duration and quality

**Sleep inertia:** impairment of alertness and performance that occurs following the transition from sleep to wakefulness

**Sleep need:** the amount of sleep needed to avoid accumulation of sleep deficiency (i.e., sleep debt)

**Sleep propensity:** the probability of falling asleep at a particular time

**Sleepiness:** subjective sensation of the desire/need to sleep; Factors that may increase sleepiness include sleep deficiency, misalignment of circadian phase, sleep inertia, some illnesses, including sleep disorders, hypnotic agents, central nervous system depressants (e.g., alcohol), and other pharmacologic agents that induce sleepiness. Factors that may reduce sleepiness include sleep, some illnesses (e.g., hypomania), wake-promoting therapeutics (e.g., caffeine), central nervous system stimulants (e.g., amphetamines), advancing age, emotional and sympathetic nervous system activation. Just as hunger is not equivalent to malnutrition, sleepiness is not equivalent to sleep deficiency. For example, individuals who are sleep deficient may not feel sleepy if they have taken a large dose of caffeine. Similarly, individuals, who are not sleep deficient, may feel profoundly sleepy due to a variety of neurohumoral pathologies and disorders.

**Suprachiasmatic nucleus (SCN):** cluster of neurons in the anterior region of the hypothalamus directly above the optic chiasm that serves as the central neural pacemaker of the circadian timing system in mammals

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