Chapter 1
Sleep Across the Lifespan

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Abstract Sleep represents a complex neurophysiological process which varies significantly across the lifespan. Sleep-wake activity is governed by a complex array of neural processes, influenced by the environment, and tightly integrated with other key biological processes such as thermoregulation, hormone release, and feeding behaviors. Changes in sleep quality and duration across the lifespan occur in part as a result of the influences of age-dependent physiological processes (e.g., menopause) or diseases (e.g., heart failure) on sleep. Conversely, changes in sleep over the lifespan impact a wide variety of physiological systems, including those important in modulating weight, metabolism, immune function, and inflammation. Thus, changes in sleep across the lifespan may influence the propensity for age-dependent diseases as well as susceptibility to chronic diseases, including diabetes, vascular disease, and cancer. This chapter reviews key changes in circadian rhythm, sleep architecture, sleep patterns, and sleep disorders across the lifespan, providing an overview of sleep neurophysiology and age-specific sleep characteristics which, as described more fully in other chapters, influence propensity for obesity and chronic diseases. A discussion of sleep in key periods in the lifespan – infants, children, adolescence, middle age, and older adulthood – is provided. A better appreciation of sleep changes across the lifespan may improve our understanding of disease mechanisms and may highlight novel approaches for improving health at critical developmental periods.

Keywords Age • Development • Sleep • Circadian rhythm • Pediatrics • Elderly

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Introduction

Sleep: Neurophysiological Overview

Sleep is a complex neurophysiological process governed by two intrinsic biological systems, which together determine the timing of sleep and wakefulness [1]. First is the homeostatic process that describes both the increasing pressure to sleep as the duration of prior wakefulness increases (process "S," shaping sleep onset times) and the dissipation of this drive in response to sleep (process "S," influencing wakening times from sleep). Age-related changes in sleep homeostatic processes contribute to the tendency for earlier bedtimes in the elderly and later bedtimes in adolescents. Second is the influence of circadian rhythms (process "C"), determined by the output from the suprachiasmatic nuclei (SCN), the body's pacemaker or biological clock, which causes well-defined diurnal fluctuations in sleep propensity and alertness (e.g., with maximal sleep propensity occurring between 2 am and 4 am). The SCN is located above the optic nerve at the base of the third ventricle, receives light input from the eye, and is close to regulatory centers in the hypothalamus. Circadian rhythms influence 24-h patterns in core body temperature and the secretion of melatonin and cortisol – key markers and modulators of the sleep-wake cycles. External influences (called zeitgebers) help align the circadian clock output with the 24-h day. The major zeitgeber is light, but factors such as feeding, temperature, and other environmental cues can influence circadian alignment.

As the brain develops and ages, the output from neural centers important in circadian and sleep-wake control varies. At 1 month of age, core body temperature has a circadian rhythm, and at 3 months of age, melatonin and cortisol are secreted in a circadian manner. The amplitude and timing of circadian rhythms change with puberty and decline with advanced age. Additionally, over the individual's lifespan, the social environment changes (work, school, and social demands), which also influence bed and wake times. Together, these intrinsic and extrinsic influences cause age-specific differences in diurnal sleep-wake activity, sleep duration, sleep architecture, and sleep propensity. Some factors also vary by gender, and many sleep traits demonstrate age differences that differ in women and men.

Sleep is characterized not only by its presence or absence (and timing) but by its quality. Sleep is composed of distinct neurophysiological stages, each described by specific patterns of brain cortical electroencephalographic activity, and associated with differences in arousal threshold, autonomic and metabolic activity, chemosensitivity, and hormone secretion [2]. Sleep is objectively measured using polysomnography (PSG), which includes scalp electroencephalography (EEG). Each sleep stage is characterized by specific patterns of EEG activity, described by EEG amplitude (partly reflecting the synchronization of electrical activity across the brain) and EEG frequency. Lighter sleep (stages N1, N2) displays relatively low-amplitude and high-frequency EEG activity, while deeper sleep (slow-wave sleep, N3) is of higher amplitude and lower frequency. Stages N1, N2, and N3 comprise non-rapid eye movement (REM) sleep (NREM). In contrast, rapid eye movement (REM)

sleep is a variable frequency, low-amplitude stage, in which rapid eye movements occur and muscle tone is low. Sympathetic tone is highest in stage REM sleep, while parasympathetic tone is highest in stage N3. In adults, over the course of the night, NREM and REM sleep cycles recur approximately every 90 min, although their composition differs across the night: early cycles typically have large amounts of N3, while later cycles have large amounts of REM. The absolute and percentage times in given sleep stages, as well as the pattern and timing of progression from one stage to another, provide information on overall sleep architecture and are used to quantify the degree of sleep fragmentation. Sleep characterized by frequent awakenings, arousals, and little N3 is considered to be lighter or non-restorative and contributes to daytime sleepiness and impaired daytime function. Higher levels of N3 are thought to be "restorative." N3, which usually predominates early in the night, reflects dissipation of homeostatic pressure; its levels may increase in response to levels of mental or physical activity over the prior day, and it is considered to be important in memory consolidation [3]. N3 sleep is also linked to somatotropin axis function (including growth hormone and IGF-1 release), and perturbations in N3 (fragmentation, restriction) have been linked to insulin resistance, diabetes, and hypertension incidence [4, 5]. REM sleep appears important for mood and in memory and is considered to be important to the developing brain, possibly because it provides neural stimulation to form mature neural connections in the newborn. Both stages N3 and REM are reduced when sleep is fragmented due to environmental disturbances, arousals related to primary sleep disorders (sleep apnea, periodic limb movements), certain medication, and substance use factors which may contribute to sleep-related adverse health outcomes.

Age is also a particularly strong determinant of sleep consolidation, state distribution, and micro-architecture [6]. Sleep-activity cycles can be identified electroencephalographically in early fetal life. As the fetus progresses towards infancy and subsequently through adulthood, there are distinctive EEG sleep architecture changes with age. As described later, sleep is characterized by marked reductions in stage N3 in adolescents, with further decreases in aging adults, with greater age-specific decreases in men than in women. Sleep also becomes less consolidated or more fragmented with advancing age. Sleep timing shows shifts from relatively "delayed" phases in adolescents to "advanced" phases in older adults; shifts in circadian phase may influence sleep architecture.

Sleep Disorders

The common sleep disorders sleep-disordered breathing (SDB), insomnia, and restless legs syndrome (associated with periodic limb movement disorder) vary across the lifespan when each may influence age-related diseases such as cardiovascular disease and diabetes.

SDB, particularly obstructive sleep apnea (OSA), is characterized by recurrent collapse of the pharynx during sleep, resulting in sleep disruption, intermittent

hypoxemia, surges of sympathetic activity, and marked swings in intrathoracic pressure. Profound physiological responses to these disturbances may result in surges in nocturnal blood pressure as well as in sustained daytime hypertension, endothelial dysfunction, dyslipidemia, an augmented inflammatory state, and insulin resistance. Patients with SDB are at increased risk for stroke, heart failure, diabetes, cancer, and mortality [7–9]. SDB occurs at all ages, although it is most common in middle-aged and older individuals. Susceptibility relates to the propensity for repetitive upper airway collapse. In any individual, propensity for airway collapse is determined by anatomic and neuromuscular factors that influence upper airway size and/or function. Chemoresponsiveness (particularly to changes in CO_2 and oxygen tensions) and responsivity to arousal also influence propensity for OSA [10]. These factors may vary across the lifespan and may vary by gender. Effects depend on the prevalence of that risk factor at given ages and are influenced by age-related changes in airway size and collapsibility, hormonal changes, and maturation of breathing control systems.

The influence of race/ethnicity on SDB varies by age, with strongest associations between SDB and race observed in children [11]. In particular, SDB is sixfold more common in African-American than white children [12]. African-American children also have a less positive response to adenotonsillectomy than do white children [13]. Other risk factors for SDB that appear particularly salient for children are low socioeconomic status and living in a distressed neighborhood [14]. Thus, minority children and those from low SES status may have a longer lifetime burden of SDB, which may contribute to an increased risk of chronic diseases.

Insomnia, identified by complaints of problems initiating and/or maintaining sleep, is common, especially among women. Insomnia is often associated with a state of hyperarousal and has been linked to increased risk of depression, myocardial infarction, and cardiovascular mortality [15]. Relative risks for cardiovascular disease for insomnia have been estimated to vary from 1.5 to 3.9; a dose-dependent association between frequency of insomnia symptoms and acute myocardial infarction has been demonstrated [16]. Insomnia may be particularly problematic at certain times in the lifespan, especially in the perimenopause period and in association with acute life stresses, such as loss of a loved one. The occurrence of insomnia during critical periods, such as menopause, may contribute to increased cardiometabolic risk factors at those times.

Short sleep duration may occur secondary to a primary sleep disorder or secondary to behavioral/social issues. Regardless of etiology, short sleep duration has been associated with increased risk of obesity, weight gain, diabetes, cardiovascular disease, and premature mortality [17, 18]. Effects are thought to be mediated by sympathetic nervous system activation, alterations of the hypothalamic pituitary adrenal axis influencing secretion of cortisol and the renin-angiotensin system, and augmented systemic levels of inflammation such as elevations in C reactive protein (CRP) levels. These physiological perturbations contribute to renal dysfunction, endothelial dysfunction, and atherosclerosis. Associations with obesity are seen across the lifespan, with evidence that associations are strongest among young children. This suggests the importance of improving sleep in individuals of all ages,

particularly infants and children. Abnormal sleep duration also is associated with low socioeconomic class, obesity, minority race, poorer mental health, tobacco use, alcohol, and poorer overall general health. Thus, there are potential additive or multiplicative effects of poor sleep with other health risk factors. Age may also modify the effects of sleep deprivation on health. For example, in an analysis data from the First National Health and Nutrition Examination Survey (NHANES-1) of nearly 5,000 adults followed for 8–10 years, a significant increased incidence of hypertension was observed in individuals 32–59 years of age reporting 5 or fewer hours of sleep per night compared to those reporting 7–8 h of sleep per night. In contrast, no associations were observed among those more than 60 years of age [19]. These data underscore the importance in quantifying thresholds for optimal sleep duration across the age span.

Age-Specific Sleep Characteristics

Infancy (Neonate to Twelve Months)

Circadian Rhythm

Prior to birth, the sleep-activity cycle is distributed across the 24-h period evenly. At birth, the day-night cycles are not yet entrained. As the central circadian pacemaker, the SCN, matures, external cues (zeitgebers) help to entrain the body into a day-night (wake-sleep) cycle. By about 6 weeks of life, the infant is more awake during the day and has more sleep during the typical night hours. By 4 months of age, most infants have "settled," meaning that they are sleeping most of the night. Additionally, at this time the two intrinsic processes that determine the timing of sleep and wakefulness, sleep homeostasis and circadian rhythm, are manifest. At 1 month of age, core body temperature displays a circadian rhythm, and at 3 months of age, melatonin and cortisol are secreted in a circadian manner. The 24-h day-night entrainment of the circadian cycle also is influenced by parents' activities and social customs.

Sleep Architecture Development

Sleep patterns in the brain start to develop at approximately 24-week post-conceptual age (PCA). This is evidenced by some neuronal electrical activity, but at this point it is very difficult to differentiate between sleep and wakefulness. Between 24- and 32-week PCA, a distinct EEG pattern called trace discontinue is seen [20–22]. Trace discontinue is characterized by bursts of high-voltage delta waves separated by prolonged episodes of electrical silence. After 32-week PCA trace discontinue matures into trace alternant, which is characterized by bursts of high-voltage delta waves interrupted by low-voltage mixed frequency activity on the EEG.

This pattern evolves into quiet sleep as the baby develops. Also around 32 weeks, active sleep can be seen on the EEG. By full term, three distinct sleep stages have developed: (1) active sleep, (2) quiet sleep, and (3) indeterminate sleep [23].

In the first few weeks of life, sleep can total up to 16 h in a 24-h period. Each cycle of sleep is 30–70 min in duration. During this time, individual sleep stages differ from that of adults. During active sleep, the infant may demonstrate some movements such as eye movements, facial grimaces, sucking, and myoclonic jerks, but these are on a background of mostly muscle atonia [20]. The hallmark of active sleep is an irregular breathing pattern. This stage is thought to develop into REM sleep as the infant gets older and the brain matures. At birth, active sleep accounts for up to 50 % of total sleep time, but this decreases to 20–25 % by 1 year of age [20, 21].

During quiet sleep, large muscle movements are generally not present, but the muscle tone on EEG is higher than seen in active sleep. The breathing pattern is regular and the EEG demonstrates trace alternant (bursts of high-voltage slow activity alternating with greatly attenuated activity). This stage develops into NREM sleep as the infant gets older and the brain matures. Trace alternant typically is not seen after about 6 weeks of life as it is replaced by stage N3 (slow-wave sleep) [20, 23].

Indeterminate sleep is the term used when polysomnography data do not clearly show changes that fit the definition of either active or quiet sleep. This usually disappears after the first month of life [20, 23].

Sometime around the second to third month of life, the EEG patterns of sleep start to take on the characteristics of adult sleep with evidence of more distinct features of stage N3 and emergence of characteristics of stage N2 sleep, namely, sleep spindles (bursts of oscillatory EEG activity) [20, 22, 23]. Although sleep architecture becomes more similar to adults, the proportion of time spent in each sleep stage differs in children and adults. As the brain matures and cortical synaptic density increases in the first year, the EEG pattern becomes more synchronized. This is an important period of neural reorganization with behavioral and physiological influences on sleep-wake patterns. By 3–4 months of age, the total sleep time starts to decrease to about 14–15 h per 24-h period, and the infant starts to show more attentive behavior during wakefulness. Also at approximately 6–8 weeks of age, the infant starts having more defined sleep and wakefulness throughout the 24-h period with more discrete daytime naps and a longer sleep period during the night. By age 6 months, this matures into the long wake period during the day and a more consolidated sleep period during the nights. In the first 8 weeks of life, the percentage of REM-active sleep and NREM-quiet sleep are about equal. Over the first 6 months of life, the percentage of REM sleep decreases and therefore the NREM percentage increases. Also, in the first few weeks of life, the infant enters sleep via REM, but this changes to NREM by about 3 months of age.

Both the sleep environment and genetic factors influence the nighttime sleep characteristics of infants. Gender does not seem to play a role in nighttime sleep duration. There is some evidence that sleep varies by ethnicity, but sorting out the effects of the environment or genetics is difficult. Sleep is also influenced by culture, such as the degree to which sleep routines are more or less structured, the occurrence of maternal-child co-sleeping, and use of sleep aids such as pacifiers.

Breathing During Sleep

Infants are particularly vulnerable to sleep disturbances, especially sleep-related breathing disorders, during the first 6 months of life. Vulnerability is likely due to anatomic risk factors (narrow, collapsible airway) and inappropriate responses to chemoreflexes. In NREM or quiet sleep, the breathing pattern is quite stable, but the respiratory rate is reduced, tidal volume is reduced, and therefore minute ventilation (respiratory rate x tidal volume) is diminished. REM or active sleep is notable for irregular breathing patterns. This is typically when periodic breathing of prematurity occurs. Infants also spend more time asleep in REM-active sleep relative to older children and adults, thus making sleep a more vulnerable time for infant's breathing [24, 25].

Sudden infant death syndrome (SIDS) is the most common cause of postneonatal infant death with approximately 2,300 deaths per year in the USA [26]. Rates are two- to threefold higher in the African-American and Native American communities. Other abnormalities of breathing during sleep in infants include apparent life-threatening event (ALTE), apnea of prematurity, and central congenital hypoventilation syndrome (CCHS) [27].

SIDS is defined as "the sudden death of any infant under one year of age, which remains unexplained after a thorough case investigation, including performance of a complete autopsy, examination of the death scene, and review of the clinical history." [26] It is more common in winter months, with infant boys, in lower socioeconomic areas and in children of parents who smoke tobacco [28, 29]. Infants born premature or with a family history of SIDS have a higher risk of SIDS. Also, infants who experience an ALTE have an increased risk. However, it is very important to note that the majority of infants who die from SIDS do not have any risk factors. The highest risk occurs between 2 and 3 months with 90 % of infants who die from SIDS being less than 6 months of age. One major risk factor that is preventable is sleep position. Since the start of the "Back to Sleep" campaign which educated parents to have the child sleep in the supine position, SIDS rates have plummeted. Other modifiable risk factors are loose bedding, soft sleep surface, bed sharing, and overheating [30]. Factors associated with reducing the risk of SIDS include use of a pacifier, breast feeding, room sharing (as opposed to bed sharing), and use of a fan in the bedroom [31, 32].

Apparent life-threatening event (ALTE) is a multifactorial paroxysmal event in an infant characterized by changes in tone, color, and breathing that is frightening to the caregiver [33]. Some descriptions include witnessed apnea, color change such as cyanosis, loss in muscle tone, and choking or gagging. The most common cause of these is gastrointestinal reflux, but may also be caused by seizures, infections, or intentional trauma. They are often benign and a link between ALTE and SIDS has not been confirmed. However, several case series documented a familial aggregation of SIDS, ALTE, and obstructive sleep apnea (in children and adults), suggesting that in some instances, each disorder may share common familial risk factors [34].

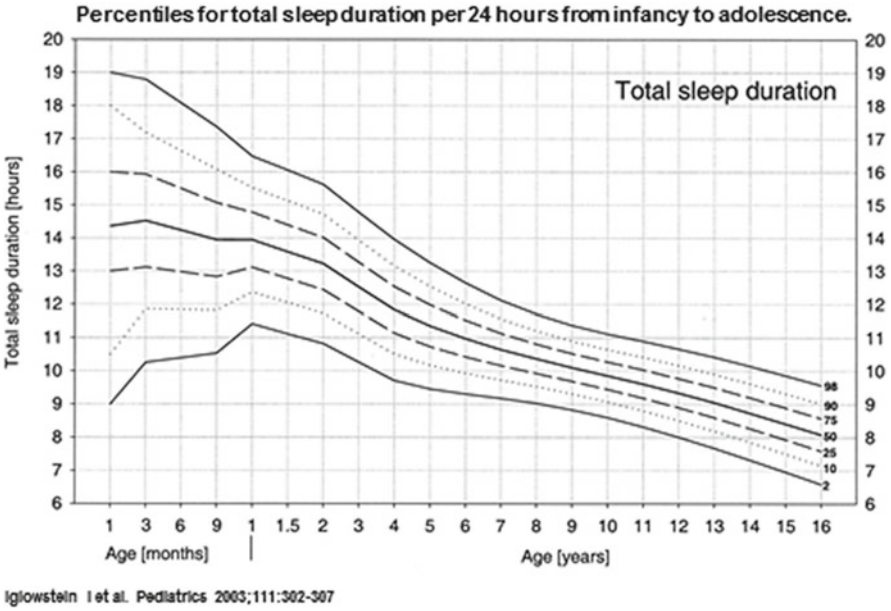

Fig. 1.1 Change in sleep duration across infancy and childhood (percentiles shown for each age, data from the Zurich Longitudinal Study; $n = 493$). The amount of time decreases as we age, with a large drop in the first year of life. A large variation among individuals is seen at all ages (From Iglowstein et al. [35])

Sleep in Early Childhood

Circadian Rhythm

In the first year of life, sleep duration averages 14 h in a 24-h period [35]. However, over the first year of life, sleep distribution changes from occurring across the 24-h period relatively regularly to, by 6 months of age, occurring predominantly at night, with approximately two naps during daytime. As children age beyond 1 year, the duration and frequency of naps reduces and thereby reduces total sleep time per 24 h to 10–13 h (Fig. 1.1). Circadian rhythm in early childhood is also influenced by external forces such as activity, exposure to light, and parental and cultural norms. In the USA, sleep duration is shorter in young children from minority ethnicity [36]. Daytime naps also differ by race and culture [37, 38]. Most children in the USA stop napping between ages 3 and 5 years. However, up to 39 % of African-American children still nap up to age 8 compared to only 4.9 % in white children [38]. The African-American children who napped had shorter nocturnal sleep duration. It is not clear whether differences in sleep patterns by race reflect genetic or environmental factors. However, shorter nocturnal sleep during infancy and early childhood is associated with increased weight at age 3 years, and thus sleep patterns in early

childhood may significantly contribute to obesity risk in minority and other children.

Sleep Architecture

In early childhood, the sleep stages are the same as adults, but the percentages are different. Young children have more stage N3 than older teenagers and adults [39, 40]. The sleep cycles are shorter than adults with each cycle occurring approximately every 40–60 min. This shorter cycle length may contribute to nocturnal arousals and awakenings. Abnormalities in sleep architecture during early childhood may contribute to daytime sleepiness and behavior and cognitive impairments.

Sleep-Disordered Breathing

Breathing is affected by sleep in early childhood and one of the more common problems is OSA. The peak age of OSA in children is in early childhood when the size of the lymphoid tissue (adenoids and tonsils) is largest compared to the size of the airway, thus leading to obstructive breathing. For children with congenital abnormalities, neuromuscular control of the upper airway is another important component. OSA is considered the severe end of a spectrum of related clinical conditions grouped together as "sleep-disordered breathing": primary snoring, upper airway resistance syndrome, and partial obstructive hypoventilation hypopneas. Seven to fifteen percent of children are habitual snorers, while 2–6 % may have frank OSA. Risk factors include enlarged adenoids and tonsils, craniofacial abnormalities, history of preterm birth, and African-American race [12]. However, obesity also increases risk of OSA in young children, and this factor may increase in relative importance as the prevalence of pediatric obesity grows [41]. Studies have also shown an increased risk of OSA in African-American children and those from lower socioeconomic status independent of obesity [14].

All of the conditions along this spectrum are associated with behavioral and cognitive impairments [42, 43]. Obstructive hypopneas and apneas with significant oxygen desaturations can lead to failure to thrive and cor pulmonale. Because of the developmental plasticity of the brain of young children, exposure to intermittent hypoxemia may be particularly deleterious [44].

Sleep in Older Children, the Influence of Puberty

Circadian Rhythm

As children enter school years, prior to the onset of puberty, the total sleep time per day decreases to 9–11 h on average and is almost exclusively during the night, with

little napping. Puberty appears to affect sleep and sleep patterns. A delayed circadian cycle is evident, corresponding to later secretion of melatonin (around 11 pm) [45]. Without societal demands, this would shift bedtime and wake times to later times. However, external factors such as early school start times require children to wake up earlier than would be set by their biological clock. This misalignment may contribute to significant sleep deprivation and sleepiness, which is further exacerbated by other societal demands (homework and school activities keeping the child up later in the night). In fact, between 50 % and 68 % of teens report sleepiness during the day, and a majority do not get the recommended 8–9 h of sleep per night [46]. These children may then attempt to make up for their sleep "debt" by sleeping longer on weekends. Increased day-to-day variability in sleep duration may further adversely affect health.

For girls, hormonal changes during puberty also affect the circadian rhythm and sleep overall [47]. Changes in sleep quality are reported to vary with phase of the menstrual cycle. The luteal phase of the menstrual cycle, when progesterone is high and the core body temperature is higher than normal, is reported to have longer onset to sleep and poorer quality of sleep.

Chronic sleep deprivation may contribute to poor school performance as well as to the neurohumoral effects associated with obesity and metabolic dysfunction. A study of adolescents (ages 13–16 years) showed that shorter sleep duration or reduced sleep efficiency was associated with higher fasting insulin levels and higher blood pressure [48, 49]. Shorter sleep is also associated with higher BMI in children and adolescents, with evidence that effects are stronger in the younger children [50]. Weight gain may be secondary to increased consumption of high fat foods and increased snacking that accompanies shorter sleep duration. There may be a stronger association between short sleep duration and obesity in boys compared to girls, although the association between increased caloric intake and short sleep appears to be stronger in girls [51].

Sleep Architecture

During the transition from adolescence to adult, several changes occur to the sleep architecture. Most notably is the significant reduction in stage N3 sleep by approximately 40 % as the child progresses through the teenage years (Fig. 1.2). This means that other stages of NREM (N1 and N2) take up more of the sleep time. Functionally this translates to the child having lighter sleep during the night and therefore is easier to arouse and awaken. Also, the biological influence of N3 on memory, learning, and hormonal control may vary across childhood as N3 decreases. Other changes in sleep architecture during this period include a longer latency to sleep onset and shorter latency to REM sleep.

At the end of puberty, the sleep cycle is very much like adults with 90-min NREM-REM sleep cycles. Menarche does not seem to substantively influence sleep architecture. Some studies, however, show that sleep spindle density is greater

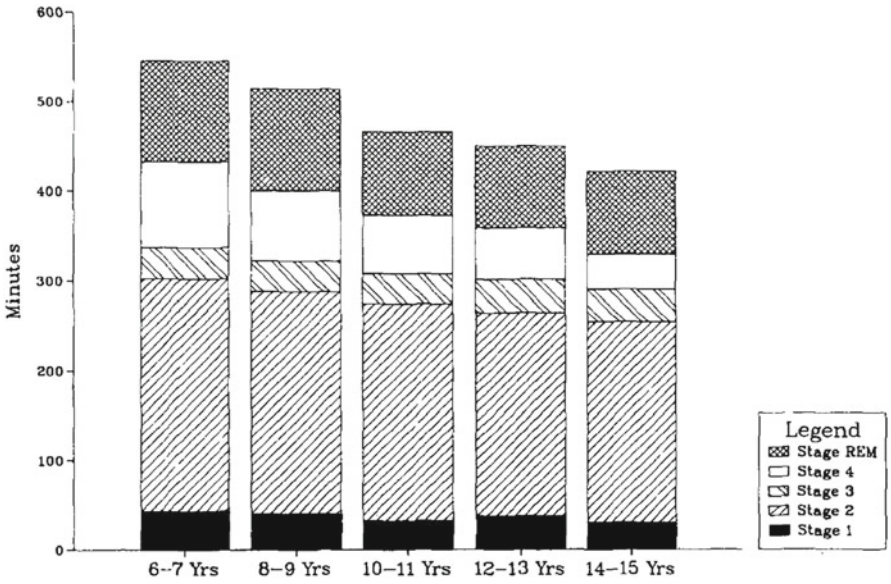

Fig. 1.2 Age-related changes in sleep architecture during childhood. Slow-wave sleep is particularly reduced during the teenage years (From Coble et al. [52])

during the luteal phase, when progesterone is highest and core body temperature is higher [53]. Since sleep spindles are considered to play a key role in modulating sleep and in sleep-dependent memory consolidation [54], this observation raises interesting hypotheses about differences in learning across the menstrual cycle.

Sleep-Disordered Breathing

Similar to SDB in the young child, SDB in the older child is a disorder characterized by repetitive episodes of upper airway obstruction, intermittent hypoxemia and hypercapnia, and snoring. However, older children may show patterns of SDB that may be more typical of that of adults (with clear apneas and hypopneas), in contrast to patterns in younger children who often may show prolonged periods of hypoventilation rather than discrete apneas. Prevalence of SDB in older children is approximately 2–3 %, but may be two- to sixfold higher in vulnerable populations such as blacks and children who were born preterm and in children from disadvantaged neighborhoods [12].

Premature birth (<36-week gestational age) may predispose to childhood SDB through in utero or early postnatal effects on craniofacial development or ventilatory chemosensitivity and load compensation. These effects may be facilitated by the plasticity of the neural control systems in infancy. In particular, in the first few days of life, maturation of respiratory chemoafferents occurs.

Exposure to hypoxia during this time, but not later, results in blunted ventilatory responses later in life [55].

Children exposed to maternal smoking are also at increased risk of SDB, possibly because of increased nasopharyngeal inflammation. Pediatric SDB also is associated with respiratory allergies and with asthma or asthma symptoms [56]. The basis for these associations is unclear, but may include increased nasal resistance causing increased negative pressure swings and collapsibility, generalized airway inflammation and narrowing, and common genetic mechanisms. Obesity is associated both with asthma and with SDB and, thus, may also partly, but not fully, explain this association.

Obesity appears to play an even stronger role in the older compared to the younger child as an SDB risk factor. Results from the Cleveland Family Study, which included children ages 4–18 years, indicate that children who are overweight are at a 4.6-fold increased risk for SDB than children who are of normal weight [11]. In contrast, in a cohort of children aged 8–11 years, risk for SDB given obesity was only 1.3 (95 % C.I: 0.55, 3.10) and not statistically significant [12]. A follow-up study of a sample of children from the latter cohort assessed at ages 13–16 years, however, showed a markedly different pattern, with an odds ratio for obesity greater than 9.0 [57]. These studies demonstrate marked differences in estimates of the influence of obesity depending on the age of the sample, with evidence of weaker associations in prepubertal children and strong associations, similar to what has been described in adults, in adolescents. Interestingly, obesity has also been associated with adenoid hypertrophy and velopharyngeal narrowing [58], suggesting that obesity may increase risk of SDB in children through several pathways.

Central obesity, as measured by the waist circumference or by visceral fat detected by specialized imaging of the abdomen, appears to be particularly important among adults as a risk factor both for SDB and for cardiovascular disease-associated comorbidities. In children, the role of body fat distribution as a risk factor for SDB has not been established. However, gender-specific patterns of body fat distribution begin to establish during adolescence, and these patterns may be useful for identifying high-risk subgroups.

The chronic comorbidities associated with untreated pediatric OSAS include cognitive deficits, behavioral problems (inattention, hyperactivity, aggression, conduct problems, attention-deficit/hyperactivity disorder [ADHD]), mood impairments, excessive daytime sleepiness, impaired school performance, and poor quality of life. However, SDB also has been associated with adverse cardiovascular and metabolic outcomes. Children with OSAS have higher levels of blood pressure, CRP, and increased insulin resistance. SDB increases risk of metabolic syndrome (characterized by dyslipidemia, central obesity, hypertension, and insulin resistance) by six- to sevenfold [57, 59]. Thus, SDB in the older child and adolescent is a potent risk factor for metabolic syndrome. Since metabolic syndrome in childhood is associated with diabetes and cardiovascular disease in adulthood, this observation underscores the importance of treating SDB early in life.

Sleep in Early to Mid-Adulthood

Circadian Rhythm

The circadian rhythm changes with age and one important change is a general shift to early sleep times (advanced sleep phase) with advancing age. While teenagers and college students have a tendency due to both intrinsic rhythm and external pressures to have later bedtimes, this starts to wane in young adulthood. This phase advance to an earlier sleep time has been referred to as "an end to adolescence" and happens at a younger age for women than for men [60]. External influences such as caffeine intake can lead the young adult to continue to have later bedtimes. However, once the person is in the adult workforce, earlier bedtimes typically are needed due to needing to wake up earlier for work (as opposed to college classes). Some studies have demonstrated that adults aged 16–54 years still get extra sleep on weekends or days off, indicating perhaps that they are not getting enough sleep on week nights. Overall, once in adulthood, most people will have a circadian rhythm such that they fall asleep in the nighttime and maintain wakefulness during the day. Notable exceptions are shift workers, comprising about 20 % of the work force (see Chap. 7).

Sleep Architecture/Duration/Stages

The sleep architecture of young adults is now solidly in a 90-min cycle with all sleep stages represented. The amount of stage N3 sleep continues to reduce at this time, at a rate of approximately 2 % per decade up to age 60 years. There is also a smaller reduction in REM sleep during early and mid-adulthood.

Once through puberty and into the 20s, most adults sleep approximately 7–8 h per night. This remains relatively constant through mid-adulthood. Young adults may still sleep a bit longer, 8–9 h for a few years. The need for sleep does not change as people progress to mid-adulthood, but the ability to maintain sleep may be affected by medical conditions and environmental influences. In fact, although average sleep duration does not change over adulthood, there is a large degree of inter- and intraindividual variability in sleep duration. Individuals who are consistently short sleepers (e.g., <6 h per night) and long sleepers (>9 h per night) and who demonstrate high between-day variability in sleep duration are at increased risk for weight gain, diabetes, and other metabolic dysfunction and chronic disease.

Pregnancy and Sleep

Pregnant women have frequent complaints related to their sleep. Many hormonal and physiological changes during pregnancy affect sleep and may be the reasons for these complaints. These can be divided up by the three trimesters of pregnancy.

During the first trimester, sleep symptoms are reported by between 13 % and 60 % of women [61, 62]. In addition, women also commonly report daytime fatigue. During the first trimester, progesterone increases and this can contribute to daytime sleepiness; increases in core body temperature also can worsen sleep quality. Changes in sleep, particularly a longer total sleep duration as well as increased awakenings and decrease in N3 sleep, have been reported to occur as early as 11–12-week gestation. Nocturia, which may interrupt sleep, may be a result of the effect of progesterone on bladder smooth muscle as well as to the effects of the growing uterus on the bladder.

Sleep often improves during the second trimester of pregnancy, but some women have persistent sleep complaints. Hormones like progesterone are leveling off during this trimester, and the uterus has now moved into the abdomen.

By the third trimester, the prevalence of sleep complaints increases to 66–97 % (Driver [61] and Lee [93]). Limited research suggests that overall objective sleep quality also is reduced, with poorer sleep efficiency, decreased REM sleep, and more awakenings at night as time in the third trimester lengthens. The uterus is now large and increases pressure on the bladder and the stomach, increasing the frequency of nocturia as well as gastroesophageal reflux, both of which may disrupt sleep. The gravid uterus also leads to significant low back pain and general discomfort while trying to sleep. During this trimester, women are at increased risk of developing sleep disorders such as restless legs syndrome (RLS) and OSA. RLS, a neurosensory disorder that often is accompanied by periodic leg movement disorder (recurrent kicks at night), likely occurs in association with iron and folate deficiency. Leg movements cause arousals, awakenings, and sympathetic surges which reduce sleep quality and can contribute to increased blood pressure. Obstructive sleep apnea may be particularly common, especially in women with high prepregnancy weights. OSA likely occurs secondary to further weight gain, body fluid redistribution, and increased nasal resistance. OSA in pregnancy is associated with an increased risk of preeclampsia and adverse fetal and maternal outcomes [63]. Gestational diabetes has been associated with OSA during pregnancy [64]. There is ongoing research on whether OSA during pregnancy contributes to persistent cardiometabolic disturbances in both mother and child.

Sleep-Disordered Breathing

SDB increases in prevalence across adulthood; however, some studies suggest a plateau may occur at approximately 65 years of age [65]. Obesity is the strongest SDB risk factor in adulthood, associated with an increased odds of SDB of four- to eightfold. Approximately 40 % of those with a BMI over 40 and 50 % of those with a BMI over 50 have been estimated to have SDB. The association between increasing BMI and SDB is shown for participants in the Sleep Heart Health Study in Fig. 1.3. Data from the Wisconsin Sleep Cohort, the Cleveland Family Study, and the Sleep Heart Health Study consistently have shown that weight gain is associated with increased severity of SDB; a 1 % increase in weight is estimated to be

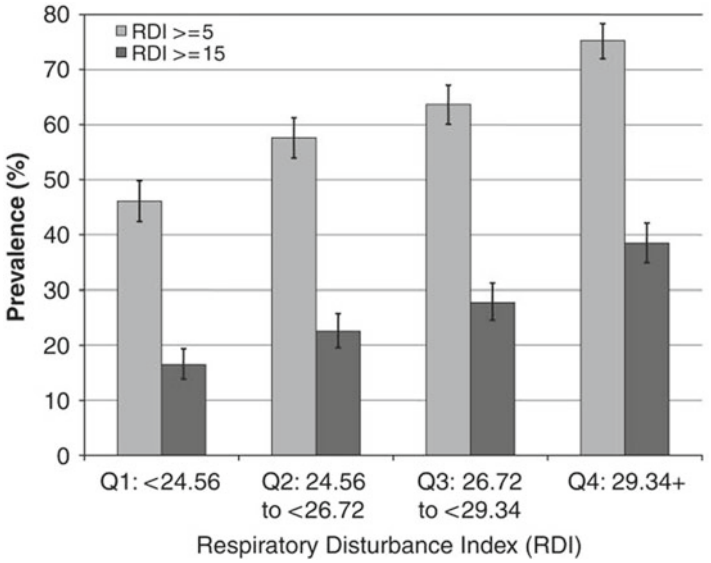

Fig. 1.3 Sleep-disordered breathing (*SDB*) prevalence estimates with 95 % confidence intervals are illustrated based upon respiratory disturbance index (*RDI*) cutoffs of 5 (*P*-value for trend <.001) and 15 (*P*-value for trend <.001) according to BMI quartile, Outcomes of Sleep Disorders in Older Men Study. Increasing SDB prevalence is seen with increasing BMI (From Mehra et al. [66])

associated with a 3 % increase in SDB severity [67–69]. Overall, the 5-year incidence of SDB is estimated to be 11 % in men and 4 % in women [67]. In middle-aged adults, visceral obesity, which is related to insulin resistance and hypercytokinemia, may be a more important determinant of SDB than total body fat or subcutaneous fat [70]. The rise in obesity in the population is expected to result in an increased prevalence of SDB. Other established risk factors for SDB include male gender, craniofacial risk factors (mandibular retrognathia, brachycephalic head form), alcohol consumption, and family history of OSA. SDB appears particularly prevalent in individuals of Asian ancestry, and this finding occurs despite the relatively low BMI in the populations studied [71]. A high prevalence of SDB in this population occurs in association with an increased prevalence of diabetes; whether the co-occurrence of these risk factors is independent or causal is not clear. However, together both conditions may increase risk for premature mortality and chronic diseases. Disease burden may be particularly great in populations at risk for both obesity and OSA related to craniofacial or soft tissue characteristics or other genetic factors, such as ethnic minorities.

Several large epidemiological studies have established that SDB is associated with significant increased incidence rates of hypertension, stroke, coronary artery disease, and heart failure [7–9, 72]. Diabetes is also associated with SDB and several moderate sized trials indicate improvement in insulin sensitivity after 1–3 months of SDB treatment with continuous positive airway pressure (CPAP) [73–76].

Meta-analyses also indicate that CPAP treatment reduces blood pressure by an average of 3 mmHg, with some evidence of larger effects in more severely affected individuals and those with higher levels of adherence [76]. A number of studies indicate that SDB is more strongly predictive of cardiovascular disease in middle-aged compared to older adults, underscoring the importance of SDB, and its key comorbidity, obesity, in middle-aged individuals.

Sleep in Older Age

Circadian Rhythm

The amplitude and timing of circadian rhythms change with advanced age [77]. Overall, amplitude is reduced and timing is advanced (sleep onset occurring earlier) by 40–60 min [78, 79]. These effects likely result from several factors, including decline in the output of SCN with neuronal aging and decreased secretion of melatonin. Also, with aging, retirement, and other lifestyle and health factors, there may be a reduced dichotomy between day- and nighttime activities, as well as inopportune light exposures, which may indirectly influence the biological clock. Visual problems such as those due to cataracts reduce the SCN's exposure to light, particularly short-wavelength frequencies which most potently influence the SCN, contributing to weakening of the circadian rhythm [80]. Sleep homeostatic pressure (process "S") responses also appear to differ with increasing age. Circadian rhythm disturbances also are common in association with neurodegenerative diseases that are common in the elderly [81]. In fact, "sun downing" is one of the most troubling symptoms of patients with Alzheimer's disease and a key reason for institutionalization. Treatment with light therapy, daytime exercise, and avoidance of daytime naps has been used with partial success for this problem [82].

Sleep Architecture

With aging, there are marked reductions in the proportion of N3 sleep, with concomitant increases in N1 and N2 sleep [83]. In addition, sleep of older individuals often is characterized by frequent arousals and awakenings and low sleep efficiency – all indications of poor sleep quality [84]. Bliwise has suggested that a reduction in percentage N3, which is correlated with many neurohumoral processes, may be a sensitive biomarker of aging [85]. Reductions in N3 may be due to age-related reductions in cortical mass, cortical metabolism, or neurotransmitter levels, changes in circadian rhythm, or other neuroendocrinological or nervous system activity. The somatotropic axis (secretory patterns of growth hormone and insulin-like growth factor) and the control mechanisms that affect stage N3 sleep are highly integrated systems that are interactive and affected by common neuroendocrinological control mechanisms. Selective reduction of N3 sleep has been associated with insulin

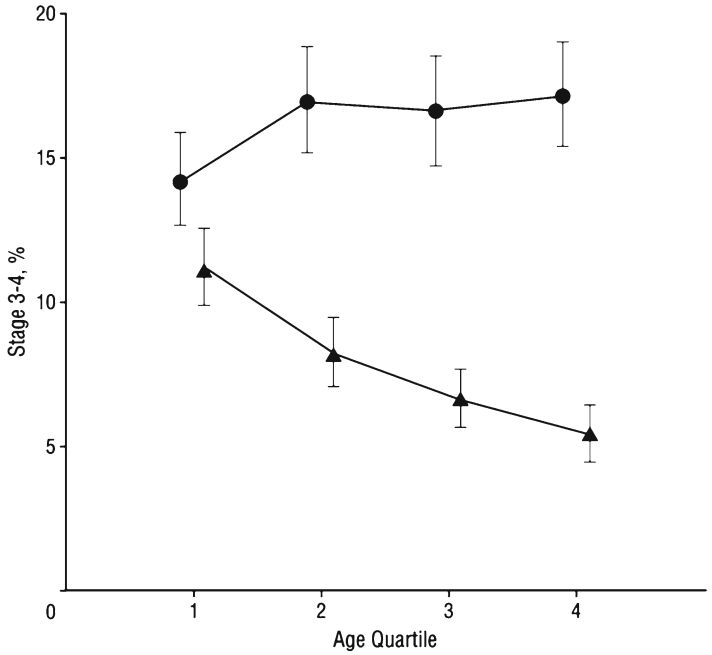

Fig. 1.4 Association between percentage stage N3 sleep in men and women in the Sleep Heart Health Study (*SHHS*) across age quartiles (≤54, >54 to ≤61, >61 to ≤70, and >70 years) for men (*triangles*) and women (*circles*). With increasing age, N3 drops markedly in men, but less so in women (From Redline et al. [83])

resistance and, in a group of older men, predictive of hypertension incidence [4, 5]. Decreased N3 also has been associated with central obesity in cohorts of older men and women, and this association was independent of total sleep duration [86]. Further understanding with changes in sleep architecture that are epiphenomena or causally contribute to the development of chronic diseases is of great importance.

Gender is a significant determinant of age-associated changes in sleep architecture. As shown in Fig. 1.4, with advancing age, N3 declines to a much larger extent in men than in women. In the Sleep Heart Health Study, after adjusting for a variety of confounders, including SDB, older women had an average 106 % higher proportion of N3 sleep and 23 % lower N1 (light) sleep [83]. Whether these dramatic differences reflect differences in cortical mass and neural connectivity or are biomarkers for other aspects of health that differentiate aging in men and women is not clear.

In addition to objective evidence of poor sleep, the prevalence of most sleep disorders increase with advancing age. Among adults over the age of 65, more than 50 % report difficulty in sleeping. In contrast to gender differences in objective sleep architecture, older women more commonly report symptoms of insomnia and poor sleep quality than older men. Sleep disturbance in older adults may be attributable to a number of factors. In addition to abnormalities in intrinsic processes related to circadian rhythm and the sleep homeostatic process, sleep is influenced by underlying

medical or psychiatric conditions, medication use, and specific sleep disorders such as insomnia, periodic leg movement disorder, and SDB. Furthermore, despite their frequency, sleep disorders are frequently undiagnosed and untreated.

Sleep-Disordered Breathing

SDB is highly prevalent in the elderly [84]; in addition to OSA, a large proportion of older individuals has central sleep apnea, i.e., more than 5 apneas per hour of sleep that are unassociated with respiratory effort and result from instability of breathing control, often due to cardiac dysfunction or cerebrovascular disease [87]. Both conditions can cause recurrent arousal, sleep disruption, and hypoxemia. A large community-based study of men more than 67 years of age, the Outcomes of Sleep Disorders in Older Men (MrOS) Cohort, estimated that the prevalence of moderate or more severe OSA was 25 % and prevalence of central sleep apnea was 7.5 % [66]. Results from this study indicate that across the age range of 67 to 90+ years, prevalence of both conditions increases with advancing age. CSA is almost twofold more prevalent in individuals with heart failure and is not associated with obesity. In contrast, OSA is associated with a 2.5-fold increased prevalence of OSA in this group – thus obesity is a significant risk factor of OSA in older individuals, although not as strong as in middle age. This may reflect the importance of other comorbidities that contribute to OSA in older individuals, including the more complex association of BMI with health as individuals age and unintentional weight loss and sarcopenia that occur in association with frailty. Like younger individuals, OSA in older individuals is associated with snoring, sleepiness, and hypertension [66]. OSA and CSA also are highly prevalent in older women; there is evidence that gender differences narrow but do not disappear with advancing age. The associations between SDB with cardiovascular disease and mortality appear to be weaker in older compared to middle-aged individuals [8]. Stroke risk is significantly increased in association with both OSA and CSA in older individuals [9].

Sleep and Menopause

Menopause has a broad range of effects on sleep [88, 89]. Some effects are associated with general physical and mental health issues experienced during the menopause transition, such as vasomotor symptoms which can be particularly disruptive to sleep. Other changes are likely due to the influence of changing hormone levels in areas of the brain that modulate sleep, many of which contain estrogen receptors. However, more consistent associations are seen between menopause and subjective as compared to objective sleep changes [90]. Because menopause is a time of frequent mood disturbance and weight gain, it is important to consider the role that sleep disruption may play in these conditions.

Estrogen and other hormonal factors may be protective for the development of SDB, and waning sex hormones likely contribute to an increase of SDB in

menopausal women. Estrogen and progesterone influence ventilatory control systems that modulate breathing during sleep. In addition, changes towards a more android (central) body fat distribution with menopause may increase airway collapsibility. In support of an importance for sex hormones in SDB is the finding that among older women, hormone replacement therapy (HRT) is associated with a lower apnea hypopnea index [91]. In addition, premenopausal women and postmenopausal women on HRT have a similar prevalence of SDB, whereas the prevalence is considerably higher among postmenopausal women not taking HRT [92]. Overall, the evidence suggests that sex hormones may influence the severity of SDB and that changes in sex hormones after menopause likely contribute to the higher prevalence of SDB in older compared to younger women.

Conclusions

Sleep is a key neurophysiological process that is manifest in utero and develops and changes across the lifespan. Brain maturation influences both sleep homeostatic and circadian rhythms which shape the timing, duration, and quality of sleep. These sleep characteristics have important influences on a wide variety of biological processes that influence weight, metabolism, and general health. These influences are notable in infancy and early childhood and have the potential to influence trajectories of weight and health across the lifespan. Sleep disorders, particularly SDB, which exposes the individual to a large number of physiological stresses that adversely affect insulin sensitivity and metabolism, also occur at all ages. Metabolic abnormalities are evident in association with even mild levels of SDB in children as well as in older populations. In considering the influence of sleep traits on health outcomes, it is important to appreciate how normative values differ by age and gender. It is also important to consider whether normal age-dependent changes in sleep traits contribute to the propensity to other age-dependent diseases, such as diabetes and cancer.

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