Circadian Rhythms in Children

# Chapter 9

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[For Springerlink]

**Abstract**

Circadian rhythms are generated by an endogenous circadian timing system. The biological clock, a key component of the circadian timing system, is anatomically located in the suprachiasmatic nucleus of the anterior hypothalamus and its functioning is grounded on a genetic-based negative feedback loop mechanism. Circadian rhythms are entrained to the 24-hour cycle by so-called Zeitgebers or synchronizers that can be environmental – such as the dark/light cycle -, social – e.g., school start time –, or biological – like melatonin.

One of the most widely investigated circadian rhythms is the sleep/wake cycle, the organization of which can be understood within the theoretical framework of the two-process model of sleep regulation. Looking at this model from a developmental perspective, it can be supposed that sleep (S) or the homeostatic process may be preponderant over the circadian (C) process in early life because homeostasis is an intrinsic basic function of living beings aimed at avoiding possible interference from the environment. The C process, on the contrary, is supposed to help the S process to gradually tune with environmental changes. It is probable that this is the reason why the C process undergoes a progressive development that is completed at the end of adolescence, changing the balance between the two processes, and becoming preeminent compared to the S process. After the C process completes its maturation, it starts to progressively weaken with age, leading to a new balance between the two processes.

**Keywords:** Circadian rhythms, children, circadian process, homeostatic process, preterm birth, chrononutrition, photoperiod at birth, individual difference, circadian preference, developmental changes

## Endogenous Origin of Circadian Rhythm: The Circadian Timing System

Circadian rhythms, which present a period of around 24 hours, are endogenously generated by the circadian timing system. The circadian timing system is composed of an input pathway, the biological clock, and the output pathway. The input pathway through photoreceptors detects and transmits information from the retina to the biological clock, which is anatomically localized in the suprachiasmatic nucleus (SCN) of the anterior hypothalamus. The biological clock then transmits its outputs to other brain areas, generating circadian rhythms, which are entrained to the 24-hour cycle by so-called Zeitgebers or synchronizers. Among the environmental synchronizers, the dark/light cycle is commonly acknowledged as the most powerful for the human species. However, at different levels, other synchronizers can be detected. For example, school start time and melatonin represent examples of social and biological synchronizers, respectively.

Although in humans the fetal SCN has been recognized at an early stage (i.e., around mild gestation) [1], at gestational term it is still largely immature. The SCN undergoes an intensive development during the very first few months of postnatal life [2]. This means that at birth circadian rhythms are still not apparent; furthermore, environmental variables during early postnatal life could importantly affect the emergence and consolidation of these rhythms.

## Examples of Interactions Between Circadian Timing System and the Environment

### *Preterm Birth*

Each milestone of the development of the circadian timing system is modulated not only by biological mechanisms, but also by interaction with the environment. One example of such interaction is represented by the preterm birth. Indeed, it has been shown that preterm infants are characterized by the earlier appearance of a 24-h sleep/wake rhythm (i.e., one of

the most widely investigated circadian rhythms) compared to full-term infants (e.g., [3]). A possible explanation of this result is that the earlier and more regular exposure of preterm infants to environmental signals such as light (e.g., the cycled light conditions) [4] and social time cues (e.g., regular feeding pattern) [5] in the neonatal care unit plays a primary role in the earlier appearance of a 24-h sleep/wake rhythm. Interestingly, results from research into the relationship between preterm birth and circadian preference suggest an association between preterm birth and an early imprinting of the SCN. Although circadian preference will be presented later in the chapter, it can basically be described as a continuum with evening types (those who prefer to perform mental and physical activities later in the day, and would rather stay up late at night and wake up late in the morning) and morning types (those who show a preference toward early bedtime and get-up time, as well as to performing demanding activities in the morning) at the extremes and intermediate-types (no clear preference toward morning or evening activities) in the middle [6]. Previous studies [7, 8] have shown an association between preterm birth and morningness preference, i.e., a preference toward an early phase of the sleep/wake cycle, which could be related to an early imprinting of the SCN in preterm born children [9].

*Chrononutrition*

Another example of interaction with the environment that could modulate the development of the circadian timing system is represented by human milk as a potent form of chrononutrition [10], which may have been shaped by evolution in aiming to transmit information to the infants regarding the time of day. It is interesting to observe that human milk differs in its composition according to the time of day. In particular, during the daytime human milk is composed of higher levels of activity-promoting amino acids and cortisol [11], which could increase alertness. On the contrary, during the nighttime, the levels of such

activity-promoting factors decrease concurrently with an increase in the levels of melatonin [12] and tryptophan, which could improve sleep and the consolidation of sleep/wake rhythms. Since breastfeeding is not always possible, knowledge regarding chrononutrition has been applied to the development of dissociated milk formulas with daytime and nighttime components, which mimic the aforementioned circadian variations in human milk. It is interesting to observe that experimental evidence seems to point out that the administration of this dissociated formula milk helps the consolidation of the sleep/wake rhythm in infants [13, 14]. In line with these observations, the study by Cohen Engler and colleagues [15] pointed out that infants who were exclusively breastfed showed a trend toward longer nocturnal sleep duration compared to those exclusively fed with artificial formula milk that was not dissociated into daytime and nighttime components.

*Photoperiod at Birth*

Photoperiod at birth represents another example of an environmental factor that could interact with and modulate the development of the circadian timing system. Indeed, it is known that annual changes in daylight occurring during the early stages of development could affect the development of the SCN, the anatomical structure that is accountable for the generation and entrainment of circadian rhythms [9]. It is thus possible that a phenomenon similar to an imprinting could happen during a sensitive stage of development immediately after birth, with the first 3 months of life suggested as a critical time for the development of sleep/wake rhythm in humans [16]. An interesting study in mice showed that perinatal photoperiod has an imprinting-like effect on the mammalian circadian clock [17], with those developing in a long photoperiod (16 hours of light and 8 hours of dark) presenting shorter circadian periods compared to those perinatally exposed to a short photoperiod (8 hours of light and 16 hours of dark). Bearing in mind that mice are nocturnal animals, these data point

out that mice exposed to a long photoperiod present a phase advance of the circadian timing system while those exposed to a short photoperiod show a phase delay. Season of birth is considered a useful marker of the perinatal photoperiod, with autumn and winter associated with decreasing and short photoperiods, while being born in spring and summer is connected with increasing and long photoperiods. During the developmental age, Touchette and colleagues [18], examining mostly Caucasian children aged between 4 and 6 years, highlighted a trend in wake-up times that were delayed in those born during spring-summer compared to those born in autumn-winter. The effects of season of birth have also been investigated with reference to circadian preference [19]. On the whole, most of the studies in Caucasian children (e.g., [20]), adolescents (e.g., [20, 21]), and young adults (e.g., [22]) found a consistent pattern of results with a higher prevalence of evening types among those born in seasons with long photoperiods, and a higher prevalence of morning types among those born during short photoperiod seasons, in line with the results observed in mice by Ciarleglio and colleagues [17]. This pattern of results could be usefully interpreted according to the photoperiod at birth hypothesis [23], with people born during long photoperiods setting their internal clocks according to longer days compared to those born during short photoperiods. As a result, the former should show a phase delay (i.e., tendency toward eveningness) compared to the latter (i.e., tendency towards morningness). Natale and Di Milia [24] successfully tested this hypothesis by assessing the relationship between season of birth and circadian preference in Caucasian university students living in the northern (Italy) and southern (Australia) hemisphere. They found an inverse relationship between hemispheres, in the direction of a higher prevalence of morning types among those born during seasons with short photoperiods and a higher number of evening types among those born during long photoperiod seasons. While the previously reviewed studies investigated Caucasian populations, works on Asiatic children [25], young adults [26], and adults [27]

failed to point to a significant effect of season of birth on circadian preference. These discrepant findings could be explained within the framework of differences between these populations in ocular photosensitivity [28] and polymorphisms of circadian clock genes [29]. As regards the circadian clock, previous studies in mammals have clarified that its functioning is grounded on a genetic-based negative feedback loop mechanism (see [30], a review). The first description of a negative feedback loop mechanism of the Period gene in drosophila by Hall, Rosbash, and Young was awarded with the Nobel Prize for Physiology or Medicine in 2017 [31]. In mammals, several circadian clock genes have been identified, such as Clock, Per1, Per2, and Per3. Although specific polymorphisms of circadian clock genes have been associated with a higher risk of diseases like multiple sclerosis [32], for example, or with the higher probability of being a morning type [33], genetic contribution is not enough to completely explain human behaviour as shown in this second paragraph about the environmental effect on the still-developing circadian timing system.

**Emergence and Consolidation of Circadian Sleep/Wake Cycle**

The emergence and consolidation of the circadian sleep/wake cycle in human infants represents an important developmental task that attracts the attention not only of parents, as expected, but also of psychologists, chronobiologists, and paediatricians. Although several studies have been carried out, the last word has yet to be said regarding the age of emergence and consolidation of the sleep/wake cycle in humans. While the emergence of a difference in activity between night and day, which could mirror the sleep/wake cycle, has already been observed in the first month of life [34, 35], the consolidation of this rhythm is thought to occur later, within the third month of life [16] or in the second half of the first year [34, 36, 37].

## Circadian Sleep/Wake Cycle and the Two-Process Model of Sleep Regulation

The organization of the sleep/wake cycle circadian rhythm can be usefully understood within the framework of one of the still prevalent theoretical models in the area of sleep research, i.e., the two-process model of sleep regulation [38, 39]. This model posits the existence of a circadian (C) process and a sleep (S) or homeostatic process that continuously interact during the 24 h cycle to auto-regulate sleep. The C process varies according to the time of day with a sinusoidal trend, reaching the acrophase at around 17:00-18:00 h and the nadir at around 04:00 h. The S process exponentially increases its value in relation to the lengthening of wake and sleep starts when a critical value is reached, i.e., when the S process comes close to the upper threshold of the C process. During sleep, the value of the S process decreases in relation to the increase of hours of sleep reaching the level observed during previous wake. The awakening occurs when the S process reaches the lower threshold of the C process. Slow-wave activity during NREM sleep is considered the main marker of the S process while the rhythms of body temperature and melatonin, which are inversely coupled, are considered the main markers of the C process. While the anatomical substrate for the S process is yet to be clearly identified, the C process is generated at the level of the SCN by the endogenous circadian clock [40]. It is possible to suggest that a unique anatomical reference center may not be necessary for the S process because such a process is more pervasive in comparison to the C process. Indeed, while the C process can be viewed as an orchestra conductor who coordinates several musicians, potentially explaining the reason why an anatomical substrate has been disclosed, the S process triggers some retroactive feedback servomechanisms, aimed at keeping the internal environment constant, and thus reducing the need for a single reference center.

## Developmental Changes According to the Two-Process Model of Sleep Regulation

Looking at the two-process model from a developmental perspective, it could be supposed that the S process may be preponderant over the C process in early life, with electroencephalographic markers of the S process appearing in the very first few months of life [41]. It is possible that the prevalence of the S process over the C process at birth could be due to the high sleep requirement in infants, which could be evolutionarily adaptive bearing in mind the potential role played by sleep at this stage of life in, for example, long-term memory consolidation [42] and cortical development [43]. Furthermore, in line with a possible earlier appearance of slow-wave sleep [44], it could be supposed, generally speaking, that from a phylogenetic point of view the S process may be preponderant over the C process in early life because homeostasis is an intrinsic basic of living beings, aimed at avoiding the possible interference of the environment. When growing up, the need for sleep decreases [45] and slow-wave activity (a marker of the S process) also decreases, particularly during puberty [43] and adolescence [43]. In line with these data, Jenny and colleagues [46] have shown that the accumulation of homeostatic sleep pressure was slower in post-pubertal adolescents compared to pre-pubertal children. This maturational change in the S process during adolescence seems to allow for the appearance of a preponderant C process. Indeed, the C process, which aims to help the S process to gradually tune with environmental changes, undergoes a progressive development that is completed at the end of adolescence [47], a period of life that is characterized by the circadian timing system's higher sensitivity to light [48]. During this precise stage of life, a phase delay in the circadian timing system [49], which has mainly been thought to be prompted by pubertal maturation, has consistently been reported, not only in humans but also in other mammalians (e.g., rhesus monkey) [50, 51]. While the C process seems prevalent in adolescence over the S process, aging is associated with a weakening of the C sleep regulation process, as pointed out by Cajochen and colleagues [52], leading to less consolidated sleep. Supporting this hypothesis, some

experimental evidence has highlighted the possible neural substrate of this age-related decline in the C process of sleep regulation. In particular, Nakamura and colleagues [53] showed a degradation of neural activity rhythms at the level of the SCN with aging in mice, in line with post-mortem studies in humans [54].

**Individual Differences in Circadian Rhythm**

Individual differences in both circadian and homeostatic sleep regulation [55] can separately contribute to the emergence of circadian preference [19], which is commonly acknowledged as one of the most robust individual differences in circadian rhythm. Although measurement of circadian preference through biological markers (for example through the recoding of body temperature) is preferable because it is more accurate, this kind of assessment is often impracticable in large-scale studies due to the high cost. For this reason, the assessment of circadian preference is commonly carried out through questionnaires, with the Morningness-Eveningness Questionnaire (MEQ) [56] being the most widely used questionnaire throughout the world. A variant of the MEQ for children and adolescents is available; this questionnaire has been successfully validated through objective external criteria such as monitoring of body temperature and actigraphic recording of sleep/wake cycle [57]. In the MEQ the use of open questions concerning the subject's ideal bedtime and get-up time allows researchers to compute the ideal midpoint of sleep, i.e., the clock time that splits the interval between the ideal bedtime and get-up time in half. The ideal midpoint of sleep is commonly acknowledged as a reliable marker of sleep timing preference because it is more strongly correlated with the overall score of the MEQ [58]. A later ideal midpoint of sleep points to a preference towards eveningness, while an earlier ideal midpoint of sleep points out a preference for morningness. From a developmental point of view, as can be observed in Figure 9.1, morningness is more prevalent than eveningness during childhood. A

shift to higher prevalence of evening types has been consistently observed in adolescents of different nationalities, leading to the supposition that mainly biological factors (e.g., pubertal maturation) may be involved in this shift. The maximum tendency toward eveningness is reached at around 20 years of age [47, 59] and afterwards, a shift toward morningness preference begins, leading to a higher prevalence of morning types in adulthood [47, 59, 60]. The end of the shift toward eveningness combined with the beginning of the shift back toward morningness at around 20 years of age has been proposed as a biological marker of the end of adolescence [47].

## Conclusions

Although the development of the circadian sleep/wake cycle is yet to be fully understood, the two-process model of sleep regulation provides a useful theoretical framework that allows us to derive some conclusions.

In early life the S process may be preponderant over the C process due to the latter being less “mature”. Indeed, the C process may be programmed to help the S process to gradually tune with the environment. The example of prematurely born infants could support the view of the gradual development of the C process, which is completed at the end of adolescence and becomes preponderant over the S process. Indeed, preterm infants’ early interaction with a sui generis environment that is characterized by a more regular temporal pattern (e.g., the regular pattern of feeding in neonatal care units) [5] may result in a reinforcement of the C process. This reinforcement of the C process could lead to the early consolidation of the circadian sleep/wake cycle in prematurely born infants [3].

As already pointed out, the topic of the emergence and consolidation of the sleep/wake cycle in infants attracts the attention of several figures, such as parents, psychologists, chronobiologists, and paediatricians. Parents, in particular, should be aware of

the potential positive outcome of circadian milk as a powerful form of chrononutrition [10] which seems a highly promising strategy to produce an early consolidation of the sleep/wake cycle [14]. Furthermore, parents should consider that “immersing” their babies into the environmental rhythmicity could promote a circadian development that is in harmony with the environment. Indeed, light is able to act on the circadian timing system even when infants are sleeping [61]. Moreover, parents should also be aware of the importance of the regularity of meals to favor a harmonious development of the C process with the environment. For example, it has been shown that skipping breakfast, an adjustable risk factor, is associated with a higher body mass index [62]. Indeed, skipping breakfast, apart from producing a lower satiety level that could explain a higher food intake, negatively affects the clock gene expression, leading to an increase in the postprandial glycemic response [63]. Since the S process is preponderant in early life, concurrently with strategies aimed at facilitating the appearance of the C process, it should be opportune to protect the homeostatic mechanisms. For example, sleep deprivation in children, the effects of which could be more detrimental than those observed in adults in which the two processes work equally, should be avoided through interventions of sleep hygiene [64] aimed at protecting the S process.

Another example of possible intervention on the C process regards adolescents. As previously highlighted, a phase delay of the circadian timing system occurs in adolescence [49] that in some cases could lead, along with other factors, to the so-called delayed sleep phase disorder (DSPD) [65]. It is known that DSPD has higher prevalence among adolescents and has several negative outcomes on health and social life [65]. A potential intervention aimed at counteracting the negative effects of DSPD is represented by light therapy, which is commonly acknowledged as an effective treatment of circadian rhythm sleep disorders [66], with light acting as a key regulator of the C process.

In spite of the phase delay in the circadian timing system that commonly occurs during adolescence, school start time (a social synchronizer) does not change according to this biological phase delay. The lack of synchrony bet ween the biological and social clock is the so-called social jetlag [67], that reaches its maximum extent during adolescence [68]. Social jetlag has been associated with several negative outcomes, such as obesity [68] and poor academic performance [69]. One potential intervention aimed at reducing social jetlag consists in acting on the C process by delaying school start time. A systematic review [70] has shown that delaying school start time by between 25 and 60 minutes can decrease daytime sleepiness and depression.

To sum up, within the theoretical framework of the two-process model of sleep regulation, two macro-categories of interventions can be suggested: on one hand, the interventions on the S process are mainly protective/collaborative, while, on the other, those on the C process are mostly educative. The interventions on the S process could be more effective if carried out in the family context; for example, the role of parents is of primary importance in order to help children to practice good sleep hygiene, thus reducing the risk of sleep deprivation. To this end, formative activities specifically addressed to parents could be devised. As regards interventions on the C process, the role of society should also be taken into account with, for example, legislative interventions aimed at delaying school start time, since this tactic has proved to be effective at reducing some consequences of social jetlag. A future research task would be to provide data concerning both types of intervention.

To conclude, this chapter has shown that, by examining the developmental changes of the sleep/wake cycle according to the two-process model of sleep regulation, some interventions can be scheduled in order to consolidate the sleep/wake rhythm in early life or to prevent/solve some issues due to the maturational changes of sleep regulation processes.

## References


1. Serón-Ferré M, Torres-Farfán C, Forcelledo ML, et al. The development of circadian rhythms in the fetus and neonate. Semin Perinatol 2001; 25: 363-370.

2. Swaab DF, Hofman MA and Honnebier MB. Development of vasopressin neurons in the human suprachiasmatic nucleus in relation to birth. Brain Res Dev Brain Res 1990; 52: 289-293.

3. Guyer C, Huber R, Fontijn J, et al. Very preterm infants show earlier emergence of 24-hour sleep-wake rhythms compared to term infants. Early Hum Dev 2015; 91: 37-42.

4. Rivkees SA, Mayes L, Jacobs H, et al. Rest-activity patterns of premature infants are regulated by cycled lighting. Pediatrics 2004; 113: 833-839.

5. Adams SM, Jones DR, Esmail A, et al. What affects the age of first sleeping through the night? Journal Paediatr Child Health 2004; 40: 96-101.

6. Natale V, Cicogna P. Morningness-eveningness dimension: Is it really a continuum? Pers Individ Differ 2002; 32: 809-816.

7. Natale V, Sansavini A, Trombini E, et al. Relationship between preterm birth and circadian typology in adolescence. Neurosci Lett 2005; 382: 139-142.

8. Strang-Karlsson S, Kajantie E, Pesonen AK, et al. Morningness propensity in young adults born prematurely: the Helsinki study of very low birth weight adults. Chronobiol Int 2010; 27: 1829-1842.

9. Kennaway DJ. Programming of the fetal suprachiasmatic nucleus and subsequent adult rhythmicity. Trends Endocrinol Metab 2002; 13: 398-402.

10. Hahn-Holbrook J, Saxbe D, Bixby C, et al. Human milk as "chrononutrition": implications for child health and development. Pediatr Res 2019; 85: 936-942.

11. Pundir S, Wall CR, Mitchell CJ, et al. Variation of Human Milk Glucocorticoids over 24 hour Period. J Mammary Gland Biol Neoplasia 2017; 22: 85-92.

12. Illnerová H, Buresová M, Presl J. Melatonin rhythm in human milk. J Clin Endocrinol Metab 1993; 77: 838-841.

13. Aparicio S, Garau C, Esteban S, et al. Chrononutrition: use of dissociated day/night infant milk formulas to improve the development of the wake-sleep rhythms. Effects of tryptophan. Nutr Neurosci 2007; 10: 137-143.

14. Cubero J, Narciso D, Terrón P, et al. Chrononutrition applied to formula milks to consolidate infants' sleep/wake cycle. Neuro Endocrinol Lett 2007; 28:360-366.

15. Cohen Engler A, Hadash A, Shehadeh N, et al. Breastfeeding may improve nocturnal sleep and reduce infantile colic: potential role of breast milk melatonin. Eur J Pediatr 2012; 171: 729-732.

16. Fukuda K, Ishihara K. Development of human sleep and wakefulness rhythm during the first six months of life: discontinuous changes at the 7th and 12th week after birth. Biol Rhythm Res 1997; 28: 94–103.

17. Ciarleglio CM, Axley JC, Strauss BR, et al. Perinatal photoperiod imprints the circadian clock. Nat Neurosci 2010; 14: 25–27.

18. Touchette E, Mongrain V, Petit D, et al. Development of sleep–wake schedules during childhood and relationship with sleep duration. Arch Pediatr Adolesc Med 2008; 162: 343–349.

19. Adan A, Archer SN, Hidalgo MP, et al. Circadian typology: a comprehensive review. Chronobiol Int 2012; 29: 1153-1175.

20. Tonetti L, Fabbri M, Martoni M, et al. Season of birth and sleep-timing preferences in adolescents. Chronobiol Int 2011; 28: 536-540.

21. Vollmer C, Randler C, Di Milia L. Further evidence for the influence of photoperiod at birth on chronotype in a sample of German adolescents. Chronobiol Int 2012; 29: 1345-1351.
22. Mongrain V, Carrier J, Dumont M. Circadian and homeostatic sleep regulation in morningness-eveningness. J Sleep Res 2006; 15: 162-166.
23. Natale V, Adan A. Season of birth modulates morningness-eveningness preference in humans. Neurosci Lett 1999; 274: 139-141.
24. Natale V, Di Milia L. Season of birth and morningness: comparison between the northern and southern hemispheres. Chronobiol Int 2011; 28: 727-730.
25. Doi Y, Ishihara K, Uchiyama M. Epidemiological study on chronotype among preschool children in Japan: Prevalence, sleep-wake patterns, and associated factors. Chronobiol Int 2016; 33: 1340-1350.
26. Takao M, Kurachi T, Kato H. Photoperiod at birth does not modulate the diurnal preference in asian population. Chronobiol Int 2009; 26: 1470-1477.
27. Huang Y, Lin D, Lu C, et al. Season of birth, sex and sleep timing preferences. Int J Environ Res Public Health 2015; 12: 5603-5613.
28. Higuchi S, Motohashi Y, Ishibashi K, et al. Influence of eye colors of Caucasians and Asians on suppression of melatonin secretion by light. Am J Physiol Regul Integr Comp Physiol 2007; 292: R2352–R2356.
29. Hawkins GA, Meyers DA, Bleecker ER, et al. Identification of coding polymorphisms in human circadian rhythm genes PER1, PER2, PER3, CLOCK, ARNTL, CRY1, CRY2 and TIMELESS in a multi-ethnic screening panel. DNA Seq 2008; 19: 44-49.
30. Hastings MH, Maywood ES, Brancaccio M. The Mammalian Circadian Timing System and the Suprachiasmatic Nucleus as Its Pacemaker. Biology 2019; 8: 13.
31. Callaway E, Ledford H. Medicine Nobel awarded for work on circadian clocks. Nature 2017; 550: 18.

32. Lavtar P, Rudolf G, Maver A, et al. Association of circadian rhythm genes ARNTL/BMAL1 and CLOCK with multiple sclerosis. PLoS One 2018; 13: e0190601.
33. Jones SE, Lane JM, Wood AR, et al. Genome-wide association analyses of chronotype in 697,828 individuals provides insights into circadian rhythms. Nat Commun 2019; 10: 343.
34. Jenni OG, Deboer T, Achermann P. Development of the 24-h rest-activity pattern in human infants. Infant Behav Dev 2006; 29: 143-152.
35. Nishihara K, Horiuchi S, Eto H, et al. The development of infants' circadian rest-activity rhythm and mothers' rhythm. Physiol Behav 2002; 77: 91-98.
36. Iglowstein I, Jenni OG, Molinari L, et al. Sleep duration from infancy to adolescence: reference values and generational trends. Pediatrics 2003; 111: 302-307.
37. Paavonen EJ, Morales-Muñoz I, Pölkki P, et al. Development of sleep–wake rhythms during the first year of age. J Sleep Res Epub ahead of print 8 September 2019. DOI: 10.1111/jsr.12918.
38. Borbély AA. A two process model of sleep regulation. Hum Neurobiol 1982; 1: 195-204.
39. Borbély AA, Daan S, Wirz-Justice A, et al. The two-process model of sleep regulation: a reappraisal. J Sleep Res 2016; 25: 131-143.
40. Schwartz MD, Kilduff TS. The Neurobiology of Sleep and Wakefulness. Psychiatr Clin North Am 2015; 38: 615-644.
41. Jenni OG, Borbély AA, Achermann P. Development of the nocturnal sleep electroencephalogram in human infants. Am J Physiol Regul Integr Comp Physiol 2004; 286: R528–R538.
42. Seehagen S, Konrad C, Herbert JS, et al. Timely sleep facilitates declarative memory consolidation in infants. Proc Natl Acad Sci USA 2015; 112: 1625–1629.
43. Kurth S, Olini N, Huber R, et al. Sleep and Early Cortical Development. Curr Sleep Med Rep 2015; 1: 64-73.

44. Cai ZJ. The functions of sleep: further analysis. Physiol Behav 1991; 50: 53-60.

45. Ohayon MM, Carskadon MA, Guilleminault C, et al. Meta-analysis of quantitative sleep parameters from childhood to old age in healthy individuals: developing normative sleep values across the human lifespan. Sleep 2004; 27: 1255-1273.

46. Jenni OG, Achermann P, Carskadon MA. Homeostatic sleep regulation in adolescents. Sleep 2005; 28: 1446-1454.

47. Roenneberg T, Kuehnle T, Pramstaller PP, et al. A marker for the end of adolescence. Curr Biol 2004; 14: R1038-R1039.

48. Crowley SJ, Cain SW, Burns AC, et al. Increased Sensitivity of the Circadian System to Light in Early/Mid-Puberty. J Clin Endocrinol Metab 2015; 100: 4067-4073.

49. Hagenauer MH, Perryman JI, Lee TM, et al. Adolescent changes in the homeostatic and circadian regulation of sleep. Dev Neurosci 2009; 31: 276-284.

50. Carskadon MA, Vieira C, Acebo C. Association between puberty and delayed phase preference. Sleep 1993; 16: 258-262.

51. Frey S, Balu S, Greusing S, et al. Consequences of the timing of menarche on female adolescent sleep phase preference. PLoS One 2009; 4: e5217.

52. Cajochen C, Münch M, Knoblauch V, et al. Age-related changes in the circadian and homeostatic regulation of human sleep. Chronobiol Int 2006; 23: 461-474.

53. Nakamura TJ, Nakamura W, Yamazaki S, et al. Age-related decline in circadian output. J Neurosci 2011; 31: 10201-10205.

54. Hofman MA, Swaab DF. Living by the clock: The circadian pacemaker in older people. Ageing Res Rev 2005; 5: 33–51.

55. Mongrain V, Paquet J, Dumont M. Contribution of the photoperiod at birth to the association between season of birth and diurnal preference. Neurosci Lett 2006; 406: 113-116.

56. Horne JA, Östberg O. A self-assessment questionnaire to determine morningness-eveningness in human circadian rhythms. Int J Chronobiol 1976; 4: 97-110.

57. Tonetti L, Adan A, Di Milia L, et al. Measures of circadian preference in childhood and adolescence: A review. Eur Psychiatry 2015; 30: 576-582.

58. Zavada A, Gordijn MCM, Beersma DGM, et al. Comparison of the Munich Chronotype Questionnaire with the Horne-Ostberg's morningness-eveningness score. Chronobiol Int 2005; 22: 267–278.

59. Tonetti L, Fabbri M, Natale V. Sex difference in sleep time preference and sleep need: a cross-sectional survey among Italian pre-adolescents, adolescents, and adults. Chronobiol Int 2008; 25: 745-759.

60. Randler C, Faßl C, Kalb N. From Lark to Owl: developmental changes in morningness-eveningness from new-borns to early adulthood. Sci Rep 2017; 7: 45874.

61. Tähkämö L, Partonen T, Pesonen AK. Systematic review of light exposure impact on human circadian rhythm. Chronobiol Int 2019; 36: 151-170.

62. Alsharairi NA, Somerset SM. Skipping breakfast in early childhood and its associations with maternal and child BMI: a study of 2-5-year-old Australian children. Eur J Clin Nutr 2016; 70: 450-455.

63. Jakubowicz D, Wainstein J, Landau Z, et al. Influences of Breakfast on Clock Gene Expression and Postprandial Glycemia in Healthy Individuals and Individuals With Diabetes: A Randomized Clinical Trial. Diabetes Care 2017; 40: 1573-1579.

64. Mindell JA, Meltzer LJ, Carskadon MA, et al. Developmental aspects of sleep hygiene: findings from the 2004 National Sleep Foundation Sleep in America Poll. Sleep Med 2009; 10: 771-719.

65. Micic G, Lovato N, Gradisar M, et al. The etiology of delayed sleep phase disorder. Sleep Med Rev 2016; 27: 29-38.

66. van Maanen A, Meijer AM, van der Heijden KB, et al. The effects of light therapy on sleep problems: A systematic review and meta-analysis. Sleep Med Rev 2016; 29: 52-62.
67. Wittmann M, Dinich J, Merrow M, et al. Social jetlag: misalignment of biological and social time. Chronobiol Int 2006; 23: 497–509.
68. Roenneberg T, Allebrandt KV, Merrow M, et al. Social jetlag and obesity. Curr Biol 2012; 22: 939-943.
69. Díaz-Morales JF, Escribano C. Social jetlag, academic achievement and cognitive performance: Understanding gender/sex differences. Chronobiol Int 2015; 32: 822-831.
70. Minges KE, Redeker NS. Delayed school start times and adolescent sleep: A systematic review of the experimental evidence. Sleep Med Rev 2016; 28: 86-95.

Figure Legend

**Fig. 9.1.** Variation of the ideal midpoint of sleep across the human lifespan. Datapoints refer to an overall number of 11.418 persons aged between 10 and 78 years old, of whom 7.225 were females and 4.193 males. The ideal midpoint of sleep reported here derives from the administration of questionnaires aimed at measuring circadian preference in several studies carried out by the research group coordinated by Professor Vincenzo Natale at the Department of Psychology of the University of Bologna (Bologna, Italy).

Chap 09 Figure

Fig 9.1