

## The interdependence of sleep and health—a commentary

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Sleep is that golden chaine  
That ties health and our bodies together.

Thomas Dekker 1570-1632  
The Great Horn Books (chapter 2)

Sleep is a very important, perhaps even the most important, biologic function to assure the well-being of humans, and other species as well.<sup>1</sup> Sleep, or lack of it, impacts greatly on other different processes, behavioral, psychological, and physiological. This may explain why the interest in sleep can be traced back many centuries BC to the early civilizations.

As stated by Dement, [1] “Interest in sleep and dreams has existed since the dawn of history. Perhaps only love and human conflict have received more attention from poets and writers.” The history of sleep has been described by many prominent investigators in sleep biology and medicine. Most interesting, and probably most comprehensive, is the *History of Sleep and Man* by Thorpy [2] that not only establishes the long scientific history of sleep, but also underscores the surge of knowledge that occurred in the 20th century and that led to the birth of a new medical specialty: sleep medicine.

Major scientific landmarks have characterized the advances of the 20th century, not least was the discovery of the electroencephalogram in man that guided the description of the architecture of sleep in the first half of the century [3-6]. Although the second half of the century brought further understanding of the neurobiology of sleep, it was characterized by the introduction of biochemistry [7] and genetics [8], and also by the study of cytokines in relation to sleep [9] to understand its mechanisms and regulation.

However, the most important advance in sleep medicine during the last few decades was the recognition of the

reciprocal impact of normal sleep and sleep disorders on somatic health conditions.

Normal sleep in healthy individuals is complex, being composed of 2 different states. The first to occur as we go to sleep is defined by non-rapid eye movements (NREM); this state is composed of 4 distinct stages indicating the progressive depth of sleep. The NREM state is followed by the state of rapid eye movements (REM) during which dreaming occurs; this state has also been said to be involved in processing emotional memory [10,11]. As sleep progresses, it is organized into cycles of NREM/REM sleep, or sleep cycles that are controlled by complex neurologic and hormonal processes. This cycling and the organization of the stages of the NREM state constitute the sleep architecture.

In man, as in other mammals, the sleep architecture, as well as the total amount of sleep, is correlated with age, sex, and body size [12]. Increasing age leads to changes in sleep continuity and to the increase of the time in light sleep while the time in deep sleep decreases. These changes appear to be more significant in men than in women. These observations, although very important, must be viewed with caution, as most of the sleep architecture alterations and other sleep disorders are associated with medical or psychological conditions that may, or may not, be recognized [13].

The International Classification of Sleep Disorders [14] identifies 88 different disorders that are grouped into 4 categories. Unfortunately, the prevalence and incidence of nearly all these conditions are not known, but there is strong evidence that they represent a significant public health concern. The importance of this concern is greatly compounded by the impact of sleep disorders on somatic disease, and conversely, by the fact that many diseases impact on sleep. This interdependence is well demonstrated by the association of sleep-disordered breathing, especially obstructive sleep apnea, with a number of somatic diseases.

Obstructive sleep apnea is by far the most prevalent of all the sleep-disordered breathing conditions. Sleep-disordered breathing is characterized by repeated periods of apnea due to upper airways collapse resulting in cessation of airflow, and/or by periods of hypopnea resulting from a partial

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<sup>1</sup> In all species in which sleep can be measured, sleep has biologic importance. In circumstances in which it cannot be measured, (ie, *Drosophila*), rest has been shown to be essential.

collapse of the upper airways. A measure called “apnea-hypopnea index” characterizes the obstructive sleep apnea syndrome that leads to blood oxygen desaturation and daytime somnolence and impaired function. The higher the index, the more severe the condition. Its severity is related to age, snoring, and excess body weight.

Obstructive sleep apnea was first described simultaneously in Germany and in France in 1965 [15,16]. Approximately 1 in 5 adults has at least mild obstructive sleep apnea, and 1 in 15 adults has moderate or worse severity. The prevalence ratio in men compared with women is about 2:1. The range of apnea-hypopnea index values in reported studies shows the difficulty to measure the prevalence of this condition, but it also clearly demonstrates the magnitude of its public health importance [17,18] in young and older subjects.

The interdependence of obstructive sleep apnea and other somatic conditions is best established by the association between sleep disorders and obesity, another well-recognized and very prevalent public health problem. Gami and collaborators [19] have published a major and comprehensive review of this association, and they have demonstrated that “obesity is the most powerful risk factor for obstructive sleep apnea.” They report that 40% of obese men and women have obstructive sleep apnea and that conversely 70% of patients with sleep disorders are obese. The risks caused by this association increase with the body mass index, and the mechanisms are many and complex. To illustrate this complexity, the authors indicate that in weight-matched subjects, fasting glucose level, insulin resistance, hemoglobin A<sub>1c</sub>, leptin, and inflammatory markers such as interleukin-6 and tumor necrosis factor  $\alpha$  are higher in those with obstructive sleep apnea. This provides evidence that in patients with obstructive sleep apnea the insulin and leptin resistances are increased as they are in patients with diabetes or metabolic syndrome. These observations demonstrate the impact of obstructive sleep apnea on metabolic functions. The concept of sleep and health interdependence is further supported by the observation that gaining weight increases the severity of obstructive sleep apnea, whereas the converse occurs by losing weight, albeit not as effectively [20]. The preceding discussion dealt with a pathologic condition, that is, obstructive sleep apnea, but it is quite significant that normal sleep, that is, without sleep-disordered breathing but of short duration, is also associated with weight gain in young adults [21].

The interdependence, perhaps even reciprocal relationship of sleep and obesity, has a critical impact on public health, first because of the number of people involved, second because of the epidemic nature of obesity in many nations of the world, and third because obesity and sleep disorders have each independently an impact on the integrity of the cardiovascular system. It has been known for years that in the absence of overweight or obesity, obstructive sleep apnea is linked to myocardial infarction, stroke, hypertension, and heart failure [22]. More recent

studies have established an association and have suggested a reciprocal relationship between atrial fibrillation and obstructive sleep apnea [23,24]. Although this linkage exists in normal weight individuals, it appears to be stronger in overweight subjects.

Especially significant is the relationship between obstructive sleep apnea, obesity, and hypertension. Several major studies have reported an independent association of obstructive sleep apnea, and hypertension, either an increase of diastolic or systolic blood pressure, or both [25,26]. Likewise, it has been reported that obesity is a major risk factor for hypertension [27]. It is therefore to be expected that the coexistence of obstructive sleep apnea and obesity compound the development and severity of hypertension [28] and of its cardiovascular complications, coronary artery disease, myocardial infarction, and congestive heart failure [27,29]. It is of course well known that elevated blood pressure is also an independent risk factor of stroke. However, recently, it has also been shown that obstructive sleep apnea increases the risk of stroke independently of hypertension [30].

Insomnia is another sleep disorder, often of psychophysiologic origin. Somatic diseases, or psychological disorders such as depression, may lead to insomnia especially in the elderly population affected by chronic disease. In turn, insomnia may increase the depressive state and compound the development and severity of somatic diseases. It has also been suggested that insomnia may impair physiological functions. Whether or not insomnia is associated with somatic or other conditions, it has a strong correlation with an impairment of quality of life (assessed by standard questionnaires), which appears to be independent of psychiatric symptoms. Although this association—insomnia and quality of life—is strong, preliminary data have suggested that quality of life is not improved by treating insomnia [31]. More recent studies of newer treatment strategies are, however, more encouraging [32].

The sleep disorders mentioned in this commentary—sleep-disordered breathing (obstructive sleep apnea) and insomnia—exemplify the importance of preventing and treating sleep disorders. Moreover, they also underscore the complexity of the mechanisms linking the sleep disorders with so many comorbidities.

Examining the impact of short duration but otherwise normal sleep, on somatic and behavioral function, gives further insight into these mechanisms. Normal sleep in adults is usually defined by a duration of 8 to 9 hours. However, societal pressure or accommodations have led to a continuous decrease of the sleep duration. In the United States, it is reported that today the average sleep duration is only 7 hours or less. Some groups of shift workers, or others such as physicians in training, experience even shorter sleep duration. Several studies have convincingly reported a close association between sleep duration and body mass index or obesity in populations ranging in age from teens to elderly [33]. Furthermore, the body weight response to sleep of

short duration is associated with significant changes in metabolic function [34]; sleep restriction to 4 hours for a week is accompanied by a decrease in glucose tolerance as well as a decrease of the insulin response to glucose, which is considered a marker of diabetes. A different study clarified these observations by demonstrating that the association of short sleep duration with risk of diabetes is most likely due to the weight gain that occurs with inadequate sleep duration [35].

The very few examples cited above vividly illustrate the interdependence of sleep, normal or disordered, specifically obstructive sleep apnea, and other somatic diseases. Many pathologic situations have been associated with sleep disorders, seemingly either as the result or the cause; among them are diabetes or its prodromic manifestations, chronic obstructive pulmonary disease, some neurologic disorders, and conditions causing pain. In addition, it is noteworthy that insomnia, a frequent but not as consequential a disorder as obstructive sleep apnea, has a considerable impact on the quality of life of the individuals who have the disorder. As pointed out, this may be linked to the progression of somatic disorders, which are the cause of insomnia to start with.

Why do we sleep is a question that has been asked by many scientists and philosophers, but as yet, no answer that is satisfactory to everyone has been proposed. Most of us see sleep as a restorative process often occurring with very pleasant dreams or emotional but illusionary journeys. The last decades have truly revolutionized our concept of sleep in the sense that we have learned that sleep is closely tied to our physiological and psychological well-being. In many ways, we could say that sleep is the “gate keeper” of many of our other functions. The advent of sleep medicine has led to discoveries from which many patients have benefited. Unfortunately, the teaching, recognition, and availability of this medical specialty are still very limited and concentrated only in the most developed countries. Yet, sleep is universal across countries as it is across species and, as a result, too many in the world are yet to appreciate the interdependence of sleep and health and to recognize what Sophocles said in the 4th century BC:

“Sleep is the only medicine that gives ease.”

Philoctebes

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