



## **A Review on Sleep-disorders in Children and Adolescents**

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### **Authors' contributions**

*This work was carried out in collaboration among all authors. Author AMMA designed and initiated the study, had written the introduction & start of the discussion, written on sleep-loss and physical-health, SRMD, RLS, PLMD, CHD, DSPS, parasomnias, narcolepsy, the epidemiology & disease-burden and the conclusion, beside the first & final draft of the manuscript. Author DS had written on classification of sleep-disorders, insomnia of childhood & obstructive sleep-apnea. Author MHH had written on pharmaceutical treatment, mood, anxiety and alcoholism & family psychiatry. Author SLH had written on developmental psychology, family psychiatry parental care, bio-psychosocial approach, psychological treatment, pediatric psychology & behavior. All authors read and approved the final manuscript.*

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### **ABSTRACT**

**Introduction:** A considerable amount of knowledge has accumulated in recent years regarding the pediatric aspects of sleep with its associated disorders being understood. Health education for parents and prospective-parents frequently pay little attention to sleep. In addition medical students and specialist-trainers receive little instruction about sleep disorders despite the fact that many of them have contact with children and adolescents who have sleep disturbances.

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The ICSD-2 describes nearly 100 sleep-disorders many of which are seen among children and adolescents.

**Aim:** The aim of this Article is to review sleep-disorders in children and adolescents, in the clinical-aspect beside epidemiology and disease-burden.

**Methodology:** Literature retrieved through Google Scholar, EMBASE, Medline and PubMed were reviewed independently by the authors towards a consensus.

**Results:** Sleep-disorders treatable, yet a large proportion remains of cases remain undiagnosed. Sleep-disorders are not uncommon among children and adolescents. Factors which contribute to sleep-disorders include extensive television viewing increased social recreational activities as well as academic demands all of which may contribute to sleep deprivation and sleep problems.

Patterns of sleep behaviours and disorders differ between children and adults.

Additionally some sleep-disorders previously thought to be seen mainly or exclusively in adults are now being recognized in children.

Explanations of the causes of sleep-problems at any age, both physical and psychological possibilities should be considered whilst at the same acknowledging that parenting practices play a major role part in children's sleep-problems.

This is important because persistent sleep disturbance can have harmful outcomes which can impact on mood, behavior, performance, social-function and physical health.

The treatment of most sleep disorders in children is, in principle, straight-forward and is more likely to be effective if it is appropriate and carefully implemented.

Medication should not be the first line treatment for a sleep disorder but instead should be used as a last resort. Behavioural methods such as sleep hygiene and counselling is preferable.

There is evidence to suggest that insufficient sleep might impair motor skills and reaction time as well as decision making and general concentration levels leading to an impact on academic achievement.

Persistent sleep-loss is becoming increasingly associated with an adult's physical health

The authors mainly discuss:

1. Insomnia of childhood
2. Obstructive sleep apnea
3. Parasomnias
4. Sleep-related movement disorders: Restless legs syndrome/periodic limb movement disorder and rhythmic movements
5. Narcolepsy
6. Delayed sleep phase disorder

**Conclusion and Recommendations:** In view of the morbidity, mortality, loss of Quality of Life, and the disease burden including the economic cost of sleep-disorders, cost-effective Prevention Programs are needed. Such Programs should educate parents, parents-to-be, teachers and healthcare professionals.

*Keywords: Sleep-disorders; health-education; children; adolescents; parenting-practices; mood; behavior; performance; social-function; physical health; medication; behavioral-methods; cognitive-function; motor-skills; insomnia.*

## 1. INTRODUCTION

Currently there is a greater empathy present in the field of Medicine for sleep-disorders that is gaining ground, however the progress is still considered to be slow. A considerable amount of knowledge has been accumulated but it remains underutilized mainly because there is a lack of awareness by both the general public and medical-professionals, particularly the field of pediatrics [1–3]. Hence knowledge in pediatric sleep-disorders lags behind that of adults.

Health education programs for parents and prospective-parents frequently miss the importance of sleep hygiene. Medical-students and specialist-trainees, including pediatricians and child psychiatrists, health visitors, child-psychologists, and teachers do not receive enough instruction despite the fact that they have frequent contact with children and adolescents with sleep disturbance, which if left untreated may result in serious health implications [1-3].

The 2005 revision of the International Classification of Sleep Disorders (ICSD-2) [6]

improved upon previous classifications but children's disorders remain inadequately referenced to.

The ICSD-2 describes nearly 100 sleep disorders - many are found in children and adolescents [1,6].

Sleep-loss and sleep disorders are common and easily treatable yet they are frequently overlooked. It is estimated that 50 to 70 million Americans (approximately 20%) chronically suffer from a disorder of sleep and wakefulness, hindering daily functioning and adversely affecting health and longevity (NHLBI, 2003) [4,5].

Such patients suffer from chronic sleep-disorders affecting daily-functioning and negatively affecting health and longevity, all of which is made worse with an ageing population (NHLBI 2003) [4,5].

Doctors seldom ask the patients about their sleep patterns (Namen et al., 1999, 2001) [4,5].

It is thought that around 80 to 90 percent of adults in the U.S. have a sleep disorder but have not been clinically diagnosed [4-7]. Not recognizing sleep-problems not only dampens diagnosis and treatment but it also impedes prevention of serious Public Health consequences.

Sleep disorders are prevalent which affect every key indicator of Public Health which include the following:

- Mortality, morbidity, performance, accidents and injuries, functioning and Quality of Life, family well-being, and health-care utilization [4, 5].

Table 1 shows the US National Sleep Foundation's Expert panel-recommended sleep-durations for the various age-groups (Hirshkowitz, 2015).

In adults, sleep-loss is defined as sleep of shorter-duration than the average minimum requirement of 7 to 8 hours per night [4,5].

One of the main consequences of sleep-loss is excessive daytime-sleepiness, but different symptoms include depressed-mood and reduced memory/concentration [4,5,8].

In the past, there have been insufficient nationally-representative surveys which offer reliable-data on sleep-patterns in populations [4,5,9,10].

Adolescents are among the population who frequently suffer from insufficient sleep. Contrary to common perceptions, adolescents need as much sleep as pre-teens [4,5,9,10].

One survey which involved 3,000 adolescents in Rhode Island observed that only 15 percent reported sleeping 8.5 or more hours on school-nights, whilst 26 percent had no more than 6.5 hours [4,5,11].

**Table 1. Expert panel recommended sleep durations**

Age	Recommended, h	May be appropriate, h	Not recommended, h
Newborns	14 to 17	11 to 13	Less than 11
0-3 mo		18 to 19	More than 19
Infants	12 to 15	10 to 11	Less than 10
4-11 mo		16 to 18	More than 18
Toddlers	11 to 14	9 to 10	Less than 9
1-2 y		15 to 16	More than 16
Preschoolers	10 to 13	8 to 9	Less than 8
3-5 y		14	More than 14
School-aged children	9 to 11	7 to 8	Less than 7
6-13 y		12	More than 12
Teenagers	8 to 10	7	Less than 7
14-17 y		11	More than 11
Young adults	7 to 9	6	Less than 6
18-25 y		10 to 11	More than 11
Adults	7 to 9	6	Less than 6
26-64 y		10	More than 10
Older adults	7 to 8	5 to 6	Less than 5
≥65 y		9	More than 9

The optimal sleep-duration for adolescents is about 9 hours per night, and is based on research about alertness, sleep-wake cycles, hormones, and circadian rhythms [4,5,12].

Among adolescents, much time spent on television and the growing social, recreational, and academic demands are reasons for sleep-loss or sleep problems [4,5,11,13].

## 2. METHODOLOGY

Literature, in the English language, retrieved through Google Scholar, EMBASE, Medline and PubMed databases were reviewed independently by the authors towards a consensus.

## 3. DISCUSSION

Unlike in adults, there are profound changes in sleep-physiology during childhood and adolescence. Rapid eye movement (REM) sleep is particularly seen a lot in very young children, possibly because of its relationship to early brain-development. The circadian body-clock needs time to develop but from about 6 months should not impede reasonably continuous night-time sleep, without the need for repeated feeds at night [1–3].

Sleep-requirements gradually reduce throughout childhood until puberty when the need for sleep increases slightly. This, combined with a physiological delay in the sleep-phase at puberty (opposite to the sleep-phase advance in the elderly) and late-night social activities, brings about potentially severe sleep-deprivation and excessive daytime-sleepiness (the delayed sleep phase syndrome, or DSPS) which can lead to educational and social difficulties in adolescence [1–3].

Certain sleep-disorders happen in a greater frequency in children and adolescents, particularly bedtime-settling and troublesome night-waking in young children (the result of not acquiring proper sleep-habits and demands on parental attention). Besides adolescent DSPS, additional examples include rhythmic-movement disorders (such as head-banging), nocturnal-enuresis, and arousal-disorders seen in pre-pubertal children mainly [1–3].

Also, some sleep-disorders previously seen mainly or exclusively in adults are now being seen in children, eg., obstructive sleep apnea,

restless legs syndrome, and periodic limb movements in sleep [1–3].

In finding an explanation for sleep-problems at any age a bio-psychosocial approach should be considered whereby physical, psychological and social factors are considered. In children, as in adults, neurological, respiratory, metabolic, endocrine, genetic, medication, or more physical-factors may have an influence. Besides that, parenting-practices play a big part in many children's sleep-problems. Parental knowledge, attitudes, and emotional-state frequently decide whether a child's sleep pattern is a problem or not. Certain parents perceive normal behavior as a problem, while many do not seek help when they should, mistakenly thinking there is no treatment available [1–3].

Where obesity is a frequent observation in obstructive sleep apnea (OSA) in adults, enlarged-tonsils and adenoids are the cause in children. Obesity may be an increasingly prominent factor at all ages, but only a small proportion of children with OSA are overweight – and conversely, very early onset may cause low body-weight from failure to thrive [1–3].

Adult OSA causes sleepiness and reduced-activity. In contrast (as in different causes of excessive-sleepiness such as narcolepsy), certain sleepy children are abnormally active. Such could lead to misdiagnosis of attention-deficit hyperactivity disorder (ADHD), and consequent inappropriate treatment with stimulants [1–3].

There remains a risk that a few sleep-disorders will be misdiagnosed at any age. Possibly, this risk is greater in children than adults because of the bigger range of clinical-manifestations and alternative-explanations for the behavioral-changes involved both as primary manifestations of the sleep-disorder but also because of secondary-complications. Narcolepsy is an example. Diagnostic-problems could also arise because polysomnography (PSG) basis for OSA and narcolepsy diagnoses are not very clear-cut and are different compared with adult-patients [1–3].

Many childhood sleep-disorders frequently resolve spontaneously unlike in adults. But in the meantime (as at any age), persistent sleep-disturbance can bring about harmful outcomes on mood, behavior, performance, social-function, and possibly, physical-health. Inadequate

management of childhood sleep-problems can also be persistent into adult-life [1–3].

But, children's sleep-disorders are generally not as much associated with psychiatric-illness. Parents should realize that the strange sleep-related behavior (in, for example, head-banging or sleep terrors) is very unlikely to mean that the child has a serious psychiatric or medical-disorder [1–3].

Differences concerning sleep and sleep-disorders between children and adults need to be discussed in both clinical practice and research [1–3].

Managing most sleep-disorders in children is, in principle, straightforward and likely to be effective if appropriately chosen and implemented with much thought [1–3].

Unfortunately though, many parents are not aware of frequently simple ways in which sleep problems in young children can be prevented or minimized by the manner the child is dealt with at bedtime or during the night [1–3].

Effective treatment in adults is not as readily achieved than in children because the origins of the sleep problem and, thus the management required, is more complicated. Particularly in the treatment of insomnia or sleeplessness, medication plays a smaller part in children than in adults. Instead, behavioral methods (also frequently important for adults) are much more appropriate and effective [1–3,14].

The relevant specialties and disciplines on which it is necessary to draw for assessment and management of children with disturbed-sleep are wider than in adults. In the case of young patients, developmental psychology, and child and family psychiatry, frequently are also needed to participate. Different influences may be conspicuous at different ages because of the many changes in a child's development [1–3].

From the early years to adolescence, about 30% of children have a sleep-disturbance which is thought of by parents, or the children themselves, to be a problem. But, because the nature of the sleep-problem varies very much with age, bedtime-difficulties and problems with night-waking are frequently seen up to about 3 years of age while, nightmares and sleepwalking for example, manifest more in older children, and

many adolescents suffer from the delayed sleep phase syndrome [1–3].

One of the key-aspects in doctor-patient care is the application of the bio-psycho-social model proposed by Engel (1977) in which the causes and treatment of medical-disorders may be considered within a framework of biological, psychological and social factors [15].

Recently Dunbar, Mirpuri, and Yip, [16] carried out a study in the US using the bio-psycho-social model in which they explored school-engagement among a group of ethnically diverse adolescents with a mean age of 14.47 years. They assessed academic outcome, sleep quality, duration and grades. They found that inadequate sleep-quality had an impact on their grades. The authors suggested that because sleep is fundamental to the development of a young-adult it is in concern to explore all causes of a sleep-disorder, including sociocultural issues. That study suggested that factors such as stress could have an impact on an individual's ability to manage conflicts and that any continual-stress could have implications from a physiological-perspective. The study could be seen as one example of how the bio-psycho-social model can be applied to understand the complex-interaction of a range of factors which could impact the health of an adolescent, particularly with regards to sleep-quality [16].

In a manner such problems are common in children overall, certain groups have sleeping-difficulties much more frequently [17].

Children with learning disabilities, different neurodevelopmental-disorders including autism, or psychiatric-conditions almost all of a time have their lives (and those of their parents) further complicated by disturbed-sleep and its aftermath. Similarly, children with types of chronic pediatric-illness [1].

Physical-factors may be big in the etiology of the sleep-problem in many of these conditions (e.g. OSA in Down syndrome) but behavioral factors (e.g. failure to develop satisfactory sleep-habits) are more common [1–3].

Similarly, these group of children can generally be expected to respond to the same of treatment as in different children, providing the treatment-program is correct for the sleep-disorder in question [1–3].

Educating parents and professionals alike would increase the use of the various type of available treatments [1–3].

“Overtired” children are difficult to handle – such children become irritable, distressed, and even aggressive, much to the concern and exasperation of the parents. In a few children, such problems are frequent and seriously disrupt family-life. As said earlier, certain young children said to have ADHD characterized by over-activity, impulsiveness, and poor concentration, actually have a primary sleep-disorder. Stimulants are not appropriate in this group and could make matters worse by escalating the sleep-problem [1–3].

As stated earlier, persistent loss of sleep can have a depressing effect and lead to the problems at home and at school particularly among adolescents [1–3].

Disturbed-sleep can affect a child's emotional-state and behavior in many different manners. Bedtime can become a source of distress when there is accompanying frightening thoughts or experiences, including night-time fears [1–3].

There is convincing evidence that insufficient-sleep can impair concentration, memory, decision-making, and general ability to learn. Performance on tasks needing sustained-attention is particularly affected – and, also those requiring abstract-thinking or creativity. In a same manner, motor-skills and reaction-time can be impaired. Studies in the USA suggest that 80% of adolescents have sleep inadequate to recommended nine hours, 25% not more than 6 hours, while more than 25% fall asleep in class. Students with insufficient-sleep achieve lower school-grades, in general [1–3].

In addition to the effect of OSA on growth in children, persistent sleep-loss in particular is being increasingly associated in adults with physical ill-health such as impaired immunity, obesity, hypertension, and diabetes [17] Children would not be free of at least some of these risks [1].

There have been reports that relationships between parent and a child with a serious and persistent sleep problem can be severely tested to the point of increased use of physical punishment in extreme cases, marital-discord and family-disharmony [1,18].

The affected child's interpersonal-problems may extend beyond her/his family. Irritable, difficult, or

disturbed behavior can affect friendships [1–3,19].

Relationships with teachers can easily suffer, particularly when teachers are not aware that behavioral-problems can be the result of inadequate or disturbed sleep, for which effective treatment can usually be provided [1–3].

There is no reason to expect that children are free of at least some of the risks to common non-communicable diseases below [1–3].

Sleep-loss affects health, and recent-research has overturned any concept that sleep-loss has no health-outcomes apart from daytime-sleepiness [4,5].

### **3.1 Sleep Loss and Physical Health**

Studies suggest that sleep-loss (less than 7 hours per night) may have wide-ranging outcomes on the cardiovascular, endocrine, immune, and nervous systems, including the following [4,5]:

- Obesity in adults and children
- Diabetes and impaired glucose tolerance
- Cardiovascular disease and hypertension
- Anxiety symptoms
- Depressed mood
- Alcohol use

Studies find that the greater the degree of sleep-deprivation, the greater the adverse-outcome [4,5].

#### **3.1.1 Sleep-loss is associated with obesity**

When a person sleeps not more than 7 hours a night, there is a dose-response relationship between sleep-loss and obesity - the shorter the sleep, the greater the obesity as measured by body mass index (BMI) [4,5].

By age 27, individuals with short sleep-duration (less than 6 hours) were 7.5 times more likely to have a bigger BMI, after controlling for confounding-factors such as family-history, levels of physical-activity, and demographic-factors [4,5,20].

#### **3.1.2 Sleep-loss is associated with diabetes and impaired glucose tolerance**

Two large epidemiological-studies and one experimental-study found an association

between sleep-loss and diabetes, or impaired glucose-tolerance.

In the Sleep Heart Health Study, which is a community-based cohort-study, adults (middle-aged and older) who reported 5 hours of sleep or less were 2.5 times more likely to have diabetes, compared with those who slept 7 to 8 hours per night [4,5].

### **3.1.3 Sleep-loss is associated with cardiovascular-morbidity**

Sleep-loss and sleep-complaints are associated with heart-attacks (myocardial infarction) and perhaps stroke, according to several large epidemiological-studies [21-26].

Several potential-mechanisms could explain the link between sleep-loss and cardiovascular-events, including blood-pressure increases, sympathetic-hyperactivity, or impaired glucose-tolerance [4,5].

### **3.1.4 Sleep-loss, mood, anxiety, and alcohol use**

Sleep-loss is associated with adverse outcomes on mood and behavior. Adults with chronic sleep-loss are found to have excess mental-distress, depressive-symptoms, anxiety, and alcohol-use [27,28,20].

A meta-analysis of 19 Original Articles found that partial sleep-deprivation changes mood to an even greater extent than it does cognitive or motor functions [29].

Several studies of adolescents, including one with more than 3,000 high-school students, found that inadequate-sleep is associated with higher-levels of depressed-mood, anxiety, behavior-problems, lower self-esteem and alcohol use [30,31,32], and attempted suicide [33].

Several types of sleep-disorders are commonly seen among adolescents. These include insomnia, hyper-somnolence disorder, narcolepsy, breathing-related disorders and restless-leg syndrome.

There are various classifications of Sleep-disorders including the International Classification of Sleep-disorders (ICSD) [6]. A modified-version found in the Nelson Textbook of

Pediatrics 20e. 2016 classifies Common Sleep Disorders in Children as [34]:

1. Insomnia of childhood
2. Obstructive sleep apnea
3. Para-somnias
4. Sleep-related movement disorders: Restless legs syndrome/periodic limb movement disorder and rhythmic movements
5. Narcolepsy
6. Delayed sleep phase disorder

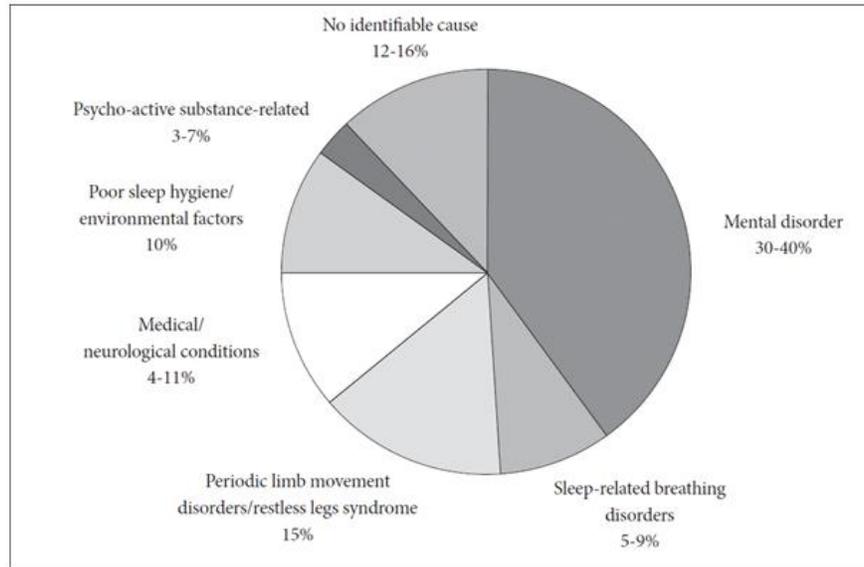
## **3.2 Insomnia of Childhood**

The most common are insomnia-disorders which may be either transient or persistent. Brief episodes of insomnia are most often associated with anxiety and among adolescents it may be due to either an anxious experience or in anticipation of an anxiety-provoking experience; a typical example might be the fear of impending exams in school or college [1].

Persistent Insomnia is a group of conditions whereby the patient may experience difficulty in falling or remaining asleep. No clear anxiety-episodes may be present but at the same time the reason(s) may be exacerbated by stress from various different sources such as personal-matters or school-stress [1].

Psycho-physiological insomnia typically presents with a complaint of difficulty in falling asleep. In such cases, it may be associated with objects associated with the sleeping-environment such as the bedroom itself or the bed. Unlike insomnia which is related to an underlying psychiatric-disorder day-time adaptation such as studies and relationships are not affected. In such cases, patients usually complain of not being able to sleep even when they force themselves. Additionally, they may also experience rumination while trying to fall asleep. Conversely, patients are able to sleep better when they are away from the usual sleeping-environment - a typical example of such could be whilst watching television [1].

Idiopathic insomnia frequently begins at an early-age and may continue throughout life. Its cause is unknown but there have been some suggestions that it might be caused by a neuro-chemical imbalance in the brainstem reticular-formation, impaired regulation of brainstem sleep-generators and basal-forebrain dysfunction [1].



**Fig. 1. The pattern of sleep-disorders observed**

Primary insomnia is when the underlying-cause is not due to either medical or psychiatric disorders. Patients complain of difficulty in initiating or maintaining sleep. Such patients are also preoccupied with getting enough sleep and may become distressed when this does not happen - in turn causing further stress [1].

Managing insomnia depends upon the duration of the affliction and how severe it is. In brief-episode insomnia, specific-treatments more than simple-advice may not be necessary. When treatment using sedative-hypnotics is needed, it must be done through good-understanding by the patients that the treatment is of a short-duration [1].

For longer-duration primary insomnia, it usually improves with sleep-hygiene and relaxation-therapy. Pharmacological-treatment such as benzodiazepines, sedating-antidepressant and zolpidem can be prescribed - but (because of side-effects) be used for short-durations only and prescribed only when psychological-treatment alone does not help the patient's condition [1].

One manner in which a sleep-disorder such as insomnia can be managed is by sleep-hygiene, which comprises a number of strategies commonly applied to foster good sleeping-habits. Such strategies include limiting the use of mobile-phones and various yet technological-equipment a few hours before bedtime, and not engaging in strenuous physical-activity. In cases

where sleep-hygiene does not work, a referral to a psychologist may also be appropriate. Additional treatment includes the use of sleep-diaries which can be used to measure the patient's understanding of sleeping-habits, besides providing an opportunity for formulating a discussion about specific underlying-matters related to the patient's complaint and condition. Psychological-treatment is often used alongside pharmacological-treatment, such as those described above [1].

### 3.3 Obstructive Sleep Apnea

OSA is found in at least four (4) percent of men and 2 percent of women in the middle-aged workforce, according to the first major United States population-based study of the condition conducted about 15 years ago [1,4,5,7].

Those prevalence-figures are based on a cut-off apnea-hypopnea index (AHI) of 5 or more, plus a requirement for daytime-sleepiness. The prevalence is greater - 9 percent of women and 24 percent of men - with the same AHI cut-off but without the daytime-sleepiness requirement [1,4,5].

Granted the epidemic-increase of obesity in recent years, these numbers could possibly underestimate the present prevalence [1,4,5].

OSA-prevalence is found to increase with age. Adults 65 to 90 years of age had a threefold greater prevalence than middle-aged adults [35],

while the prevalence in children is estimated around 2 percent [36,37], with larger estimates seen in ethnic-minorities in the US [37,38].

Under-diagnosis of OSA is common, with only about 10 to 20 percent being diagnosed in adults [7]. Not more than 1 percent of older-adults in primary-care are seen referred for polysomnography [39], although these numbers could have increased in recent-years because of increased public-knowledge of the disease.

Since data on children such as above is not forthcoming in literature-searches, the authors here use data on adults in an attempt to reflect on the overall situation.

In the same manner, children's OSA frequently remains undiagnosed also, partly because the implications of snoring frequently being not recognized by pediatricians.

Although OSA could be found in children of all ages, it is most common among preschool-ages - a time coincident with tonsils and adenoids being largest in size relative to the underlying-airway (Jeans et al., 1981).

The main risk-factor for OSA in children is tonsillar hypertrophy, although OSA may also be found in children with congenital and neuromuscular disorders, and in children born prematurely (Rosen et al., 2003).

Asthma, a common childhood respiratory-illness, is also seen associated with OSA in children (Sulit et al., 2005).

Treatment modalities in OSA in children include [40]:

- Medications. Topical nasal steroids, such as fluticasone (Dymista, Flonase Allergy Relief, Xhance,) and budesonide (Rhinocort), eases sleep-apnea symptoms for some children with mild, obstructive sleep-apnea. For children with allergies, montelukast (Singulair) helps relieve symptoms when used alone, or with nasal-steroids.
- Removal of the tonsils and adenoids. Adeno-tonsillectomy improves OSA by opening the airway. Yet different forms of upper-airway surgery may be required based on the child's condition.
- Positive airway-pressure therapy. In continuous positive airway-pressure

(CPAP) and bi-level positive airway-pressure (BPAP), small machines gently blow air through a tube and mask attached to the child's nose, or nose and mouth. The machine sends air-pressure into the back of the child's throat to keep the child's airway open. Positive airway-pressure therapy is the commoner modality. Proper fitting of the mask, and refitting as the child grows, can help the child tolerate the mask over the face.

- Oral appliances. Oral appliances, such as dental-devices or mouthpieces, move the child's bottom-jaw and tongue forward to keep the upper-airway open. Only some children benefit from such devices.
- Avoiding airway irritants and allergens. All children, but especially those with pediatric obstructive sleep-apnea, must avoid tobacco-smoke or the various indoor allergens or pollutants, as such could cause airway irritation and congestion.
- Weight loss. The child must lose weight when she/he is obese, based on diet and nutrition information, including referral to various specialists having expertise in managing obesity.

The CHAT Study (Marcus CL 2013) showed that in comparing a plan of watchful-waiting, surgical-treatment for the obstructive sleep apnea syndrome (OSAS) in school-age children did not significantly improve attention or executive-function as measured by neuropsychological-testing, but did reduce symptoms and improve secondary-outcomes of behavior, quality of life, and polysomnographic findings - thus providing evidence of beneficial outcomes of early adeno-tonsillectomy [41].

The Tucson Children's Assessment of Sleep Apnea Study (TuCASA) (Budhiraja R and Quan SF, 2009) is a longitudinal cohort-study of 503 6-12 year old Caucasian-children and Hispanic-children who had polysomnography and neurocognitive testing initially. Subsets of the cohort had additional MRI-imaging and pulmonary physiologic-testing. Cross-sectional analyses indicated that Sleep-disordered Breathing (SDB) is associated with behavioral-abnormalities, hypertension, learning-problems and clinical-symptoms such as snoring and excessive daytime-sleepiness. The Study feels future follow-up of the cohort will assess the impact of SDB on subsequent childhood-development [42].

**Table 2. ICSD-3 classification of the SRMDs**

1.	Restless legs syndrome
2.	Periodic limb movement
3.	Sleep-related leg cramps
4.	Sleep-related bruxism
5.	Sleep-related rhythmic movement disorder
6.	Benign sleep myoclonus of infancy
7.	Propriospinal myoclonus at sleep onset
8.	Sleep-related movement disorder due to a medical disorder
9.	Sleep-related movement disorder due to a medication or substance
10.	Sleep-related movement disorder, unspecified

**3.4 Sleep-related Movement Disorders**

ICSD-3 characterizes Sleep-Related Movement Disorders (SRMDs) by simple, often stereotyped movements occurring during sleep [43].

**3.5 Restless-leg Syndrome**

RLS, or the Willis Ekbohm syndrome, is a group of chronic neurological-disorders characterized by feeling of discomfort in the legs and an uncontrollable-need to move them.

A family-history is found in 72% of cases with the mother three times more likely to suffer from the disorder than the father [44]. The mode of inheritance is complex.

Iron stores may be low. Diabetes mellitus, end-stage renal disease, cancer, rheumatoid arthritis, hypothyroidism and pregnancy may be associated, as well as drugs like nicotine, antihistamines, tricyclic antidepressants, selective serotonin reuptake inhibitors, cimetidine and caffeine [45,46].

RLS is underdiagnosed in children, often mistaken as growing-pains. It is seen in 1-6% of children. It is more common in females. There is association with negative behavior and mood, and decreased cognition and attention. Greater prevalence of RLS is seen in those with attention-deficit/ hyperactivity disorder (ADHD).

The symptoms are worse when resting and in the evening or bedtime, and when travelling in a car for prolonged periods. These are partially relieved by movement such as stretching, walking, rubbing or massage [45].

Children wake up frequently from sleep, and may be tired and inattentive during the day.

The International Restless Legs Study Group [47] (IRLSSG) reviewed the 1995 diagnostic-

basis (criteria) for RLS and developed new consensus. These are shown in Table 3 here below. The separate set for the diagnosis of RLS in children, found in ICSD-2, has been eliminated. Pediatric diagnostic-considerations are discussed in the ICSD-3 developmental-section of RLS [43].

Diagnosing RLS in children can be difficult as it depends on the patient’s ability to describe core-symptoms. Diagnosis can be made if the history is consistent with the condition, and at least two of the following are present [6]:

- A sleep disturbance,
- A first-degree relative with RLS, or
- Five or more periodic limb-movements per hour of sleep during poly-sonography

Conservative treatment includes avoiding exacerbating factors.

With Periodic Limb Movements (PLMs) < 5 per hour, no treatment is recommended. With PLMs greater than 5 per hour, the decision to treat depends on nocturnal-symptoms and daytime-sequel [45].

The acronym AIMS represents the approach to treatment of RLS:

- A: Avoidance of exacerbating factors – caffeine, drugs
- I: Iron supplement when indicated if serum ferritin < 50 ng/ml. Ferrous sulfate 3-6 mg/kg/day for duration of 3 months is adequate.
- M: Muscle activity, increased physical activity, muscle relaxation, hot or cold compresses
- S: Sleep – regular and appropriate sleep-for-age

There aren’t any medications approved for treating restless legs syndrome in children. But drugs that increase CNS dopamine levels, such

as ropinirole and pramipexole are found effective in adults [45].

### 3.6 Periodic Limb Movement Disorder

Periodic limb-movement disorder (PLMD), previously known as sleep-myoclonus or nocturnal-myoclonus, comprises repetitive limb-movements during sleep that disrupt sleep. Usually involves the lower-limbs, rarely the upper-extremities. The movements may involve extension of the big-toe, or flexion of ankle, knee and hip. The movements happen during light non-REM sleep, are repetitive and are separated by intervals of 5-90 seconds with night-to-night variability in the frequency of limb-movements. PLMD may be asymptomatic [48]. Patients are usually not aware until a parent, family-member or partner calls attention to the limb-jerks, restless-sleep, moving-around or falling-out of bed. Frequent awakenings, non-restorative sleep, daytime-fatigue, daytime-sleepiness are the usual symptoms [45].

Prevalence of PLMD is not known but it can be found at any age – and, not gender-related. It is found in 80% of those with RLS and in 30% of those aged > 65 years. It is found commonly together with narcolepsy and REM behavior-disorder, OSA and during PAP-therapy. The associated medical-conditions are uremia, diabetes mellitus, OSA, and spinal cord injury. Symptoms may be aggravated by antihistamines, antidepressants, and antipsychotics.

PLMD is diagnosed when the following are present [48,49]:

1. PLMs documented by polysomnography
2. PLMs exceeds norms for age (>5/h for children),

3. Clinical sleep-disturbance or daytime-fatigue
4. Absence of any different primary sleep-disorder or reason for PLMS, including RLS and OSA

Diagnostic-workup includes a good clinical-history and a thorough neurological-examination, followed by an overnight-polysomnogram (PSG). Respiratory-monitoring is required to rule out sleep-disordered breathing as a cause. Thyroid function, magnesium levels, folic acid, and vitamin B<sub>12</sub> levels need to be determined [50,51].

Avoidance of caffeine, chocolate, tea, coffee, soft drinks is needed. Antidepressants can cause worsening. Regular and appropriate sleep-forage is encouraged. Dopamine-agonists are used as the first-line of defense; various drugs including anticonvulsants, benzodiazepines, and narcotics are used. No cure is available - medical treatment needs to be continued for relief [50,51].

### 3.7 Central Disorders of Hypersomnolence

The International Classification of Sleep Disorders characterizes central-disorders of hypersomnolence (CDH) by their feature of excessive daytime-sleepiness (EDS) or hypersomnolence that is defined as daily-episodes of an irrepressible-need to sleep or daytime-lapses into sleep that is not attributable to the different sleep-disorders, e.g., sleep-related breathing-disorders or abnormalities of circadian-rhythm, and interferes with normal daily-functioning [43].

**Table 3. International restless legs syndrome study group consensus diagnostic criteria for restless legs syndrome**

1.	Urge to move legs, usually but not always, accompanied by or felt to be caused by uncomfortable and unpleasant sensations in the legs
2.	Urge to move legs, and any accompanying unpleasant sensations begin or worsen during periods of resting or inactivity such as lying down or sitting
3.	Urge to move legs, and any accompanying unpleasant sensations are partially or totally relieved by movement, such as walking or stretching, at least while activity continues
4.	Urge to move legs, and any accompanying unpleasant sensations during resting or inactivity only seen or are worse in the evening or night rather than during the day
5.	Finding above manifestations are not solely accounted for as symptoms primary to different medical or a behavioral condition (e.g., myalgia, venous stasis, leg edema, arthritis, leg cramps, positional discomfort, habitual foot tapping)

In classifying, CDHs are commonly caused by:

1. Intrinsic-abnormalities of the CNS that controls the sleep-wake mechanism, e.g. narcolepsy and idiopathic hypersomnia (IH).
2. Extrinsic-causes, e.g. Kleine-Levin syndrome, hypersomnia due to medical or psychiatric disorders, ingestion of medications or substances, and insufficient-sleep syndrome [43].

Diagnosis of narcolepsy and idiopathic hypersomnia (IH), requires demonstration of objective-sleepiness by the Multiple Sleep Latency Test (MSLT). A mean sleep-latency of 8 min on the MSLT is required for diagnosis. This criterion remains unchanged from the ICSD-2 [52,53]. Care needs to be exercised when making the diagnosis, since abnormal MSLT-findings may be present in actually normal, sleep-deprived subjects, especially those with longer sleep-requirements [54]. Conversely, some with genuine CDH may not achieve MSLT latencies of 8 min [55]. This test could be repeated subsequently to confirm objective-a sleepiness.

### 3.8 Narcolepsy

Narcolepsy is characterized by the classic tetrad of excessive daytime-sleepiness (EDS), cataplexy (brief sudden loss of muscle tone), hypnagogic/hypnopompic hallucinations, and sleep-paralysis. Children rarely manifest all four (4) symptoms [56,57].

Diagnosis requires EDS-presence, that is the primary symptom of narcolepsy, to be present for at least 3 months. Severe EDS leads to involuntary-somnolence that interferes with normal-functioning such as working, walking, driving, eating, or talking. Sleep-attacks characterized by regular severe sudden-episodes of falling asleep are seen.

Mild catalepsy presents with partial-loss of tone, e.g. head-nodding, altered-speech or knee-buckling, while severe-disease is generalized and leads to falls. Respiration and extra-ocular movements are spared. Attacks may be triggered by emotions such as laughter or anger [56,57].

Sleep-paralysis manifests as the inability to move upon awakening, or less commonly, upon falling asleep with consciousness intact. Such may be accompanied by hallucinations. The paralysis

happens not so frequently when the sleeping-position is uncomfortable. It does not affect the respiratory or extra-ocular muscles, and can be relieved by sensory-stimuli, e.g. touching or speaking to the affected-person [56,57].

The main-symptoms of narcolepsy in children are restlessness and motor over-activity, accompanied by academic-deterioration, inattentiveness, and emotional-lability. At early stages, children with narcolepsy and cataplexy display a wide range of atypical cataleptic motor-disturbances like hypotonia or active perioral-movements, dyskinetic-dystonic, or stereotypic-movements.

Cataplectic-facies have been described in children with narcolepsy and cataplexy, usually at disease-onset. The typical facies include repetitive mouth-opening, tongue-protrusion, and ptosis. The usual triggering-emotions, such as laughter or joking, are not always present, causing difficulty with diagnosis [57].

Physical-examination findings are normal in patients with narcolepsy. A careful neurologic-examination is needed to exclude different causes. Obesity may be associated with the disorder. During a typical episode of cataplexy, patients typically demonstrate atonia of muscles of the limbs and neck and loss of deep-tendon reflexes [57].

In differential-diagnosis, Idiopathic hypersomnia (IH) and narcolepsy present similarly and can be difficult to distinguish. But, IH does not have sleep-onset rapid eye movement (REM) period, and the naps are unrefreshing. In addition, IH is not associated with cataplexy [57,58].

As part of investigations, an overnight polysomnogram (PSG) followed by a MSLT provides strong evidence of narcolepsy, while excluding the different sleep-disorders such as IH.

Measurement of hypocretin (orexin) concentration in the cerebrospinal-fluid (CSF) may help establish the diagnosis of narcolepsy when the concentration is lower than 110 pg/mL, but, high CSF hypocretin concentration does not exclude the diagnosis [59].

Imaging-studies are generally unrevealing, but MRI is useful in excluding rare-cases of symptomatic-narcolepsy. Structural-abnormalities of the brain-stem and diencephalon may present as idiopathic-narcolepsy. In patients with

secondary-narcolepsy, MRI of the brain may show abnormalities depending on the underlying cause.

Human leukocyte-antigen (HLA) typing is more useful for excluding the diagnosis if the patient does not have either DQB1\*0602 or DQA1\*0602, but is not so valuable for confirming the diagnosis, since HLA-DR2 and DQw1 are present in 20-30% of the general population.

An individualized multidisciplinary approach is recommended in treatment of narcolepsy.

1. **Sleep hygiene:** Most patients benefit from a regular nightly sleep-schedule of 7.5-8 hours, and scheduled-naps during the day.
2. **Diet & activity:** Avoiding heavy-meals, and diets high in refined-sugars, may improve daytime-sleepiness. Participating in an exercise-programs helps. There is need to avoid driving, operating heavy-machinery, or undertaking potentially hazardous-activity that may place lives at risk. There is a need to wear a life-preserver when involved in water-activities and never to perform water-activities solo. There is a need to educate the group about narcolepsy and cataplectic attacks and to refrain from activities when feeling drowsy.
3. **Pharmacologic treatment:** Presently, there isn't any FDA-approved pharmacotherapy available for children with narcolepsy. But, medications, methylphenidate and modafinil have proved effective in children 6-15 years old [60].
4. **Non-pharmacologic measures:** This includes emotional support, career or vocational counseling, assisting with documentation for educational-enrolment, insurance, disability-forms, and attaining a driver's license. There is a need to inquire about high-risk behaviors such as alcohol and drug use that could exacerbate symptoms, depression, family-conflict, and various psychosocial-problems
5. **Long-term monitoring:** Children with narcolepsy need to be followed up by both the primary-pediatrician, pediatric-neurologist, and sleep-medicine specialist when available for monitoring drug-effectiveness, response to treatment, and potential adverse drug-outcomes. This

should be done annually, and every 6 months if the patient is on a stimulant. He should also contact a narcolepsy support-group for support.

### 3.9 Delayed Sleep-phase Disorder

In older children and after, early-morning wakening may be part of an anxiety or depressive-disorder. If not, the child could have been woken-up too early by noise, or various different environmental-factors which intrude into her/his sleep [1,4,5].

The generally very efficient sleep of pre-pubertal children changes to not so satisfactory sleep in adolescence for both physiological and psychosocial reasons [1,4,5].

Worries, anxiety, and depression are commonly-quoted reasons for the difficulty in sleeping at this age. Nicotine, alcohol, and caffeine-containing drinks, besides illicit-drug use, are additional possible influences [1,4,5].

But, inability to get off to sleep and to wake up in the morning is frequently part of the Delayed Sleep Phase Syndrome (DSPS), which was discussed earlier. This condition, which particularly common in adolescence, potentially very much disrupts education and social-mingling. As such, it needs be discussed further. DSPS is commonly misconceived as not a sleep-disorder.

The problem usually arises from the sleep-phase delay at puberty, besides habitually staying-up late for social or such reasons, especially on weekends or during holidays. The result is that it becomes not possible to go to sleep earlier by choice [1,4,5].

The manifestations of DSPS are persistently severe difficulty getting to sleep (possibly until well into the night), uninterrupted sound-sleep for just a few hours, but then great difficulty getting up for school, college, or work because of not having enough sleep. This causes sleepiness and under-functioning, especially during the first part of the day. The abnormal sleep-pattern is maintained by sleeping in very late when able to do so on weekends and during holidays [1,4,5].

"Chronotherapy" includes gradually changing the sleep-phase to an appropriate-time. In cases where the phase-delay, is about 3 hours (or less), bedtime can be gradually brought forward. More severe-forms of the disorder require

progressive sleep-phase delay in 3-hour steps round the clock until a satisfactory-timing is achieved which then needs to be fixed [1,4,5].

Additional measures to maintain the improved sleep-schedule include early-morning exposure to bright-light and firm-agreement with the adolescent to maintain a new pattern of social-activities and sleep. Melatonin in the evening may also help [1,4,5].

Difficulties achieving and maintaining an improved sleep-wake schedule by these means are compounded if there is a vested-interest in maintaining the abnormal sleep-pattern, for example, to avoid school ("motivated sleep phase delay"). Psychological problems, including depression, may impede treatment success. The teenager's reluctance to go to bed earlier and to get up at the required time is frequently misinterpreted as "typical difficult adolescent behavior" causing trouble in the family. If not, the condition could be mistakenly viewed as the usual form of school non-attendance, primary-depression, or substance-misuse [1,4,5].

### 3.10 Parasomnias

Parasomnias are repetitive unusual behaviors or strange experiences that happen just before, during, or arising out of sleep, or on waking. The many parasomnias (some primary sleep-disorders, others secondary to medical or psychiatric-conditions) now officially recognized (over 30 in ICSD-2) indicate how commonly and in many ways (some subtle, others dramatic) sleep can be disturbed by episodic-events [1,4,5].

Confusing between the different parasomnias seems common. For example, in pediatric textbook-accounts, sleep-terrors and nightmares (two very different types of parasomnia) are mistaken (for one another). Indeed, sometimes there is an inclination to call all dramatic-parasomnias a nightmare. Correct diagnosis is very necessary because different parasomnias each have an own significance, and call for contrasting-types of advice and treatment. The following brief-account is concerned with the main-manifestations to be recognized in reaching the correct diagnosis. Emphasis is placed on just some of the more dramatic parasomnias (namely arousal disorders, nightmares, and sleep-related epileptic seizures) as these frequently cause most confusion and concern [61]. Frequently, an accurate diagnosis can be made by means of a

detailed-account of the subjective and objective sequence of happenings from the onset of the episode to its resolution, and of the circumstances in which the episode happened, including its duration and timing. Audiovisual-recording (including by means of home-recording by parents) can be very informative and frequently adds details that are missed in descriptions given at consultation [1,4,5].

For the most part (seizure-disorders generally being a main exception), physiological-recordings are required only when clinical evaluation is inconclusive or where the child might have more than one type of parasomnia. The meaning of the three categories is as follows [1,4,5].

The term "arousal disorders" refers to childhood confusional-arousals, sleepwalking (calm and agitated forms of which are described) and sleep-terrors. Nightmare is the proper better term. As sleep-related epilepsy covers a number of seizure-disorders of different types, permissible-generalizations are limited [1,4,5].

The following types of epilepsy are, to varying degrees, related to sleep. The first four (4) types have been classified as benign in the sense that, despite the focal-origin in the brain, such are not typically the result of a structural abnormality and can be generally expected to remit spontaneously in time [62]. All five types can readily be confused with non-epileptic-parasomnias as their clinical-manifestations can be complex and dramatic.

Benign partial-epilepsy with Centro-temporal-spikes (Rolandic epilepsy) is a frequent form of childhood-epilepsy where 75% of patients have their seizures entirely during sleep. The seizures involve distressing oropharyngeal-facial movements and sensations in line with the anatomical-origin of the seizure some doubt exists about their entirely benign-nature [63].

Apparent terror and screaming happen in benign-epilepsy with affective-symptoms [64].

The child's reactions to the complex visual-experiences (including hallucinations) that can happen in benign occipital-epilepsy may involve dramatic-behavior.

In the Panayiotopoulos syndrome, seizures frequently involve distressing vomiting and various autonomic symptoms.

Nocturnal frontal-lobe epilepsy (NFLE) deserves special-mention because its clinical-manifestations make it particularly prone to misinterpretation as parasomnias. This also happens in children, although this is mainly described in adults [65].

It is now realized that NFLE can present in a variety of forms [66], but a usual variety is frequently misdiagnosed mainly because the complicated motor-manifestations (eg kicking, hitting, rocking, thrashing, and cycling or scissor movements of the legs) and vocalizations (from grunting, coughing, muttering or moaning to shouting, screaming, or roaring) that characterize many attacks. As such, these are very different from the various seizure-types. The abrupt onset and termination, short-duration of the attacks (different from seizures of temporal lobe origin) and, sometimes, preservation of consciousness can also suggest a non-epileptic (even attention-seeking) basis for the attacks.

In the first instance, diagnosis is based on being knowledgeable of this form of epilepsy and

recognition of its clinical-manifestations. EEG-recordings, even during the episodes, are of limited diagnostic-value.

The distinction between epilepsy and the different parasomnias is not without difficulty. Recently, the Bologna's group of clinical-researchers attempted to set out clearly the (mainly clinical) criteria for distinguishing between NFLE and the various parasomnias [67].

### 3.11 The Epidemiology and Disease-burden of Sleep-disorders in Children

The Fig. 2 shows the age-composition of the US population in the years 2000 and 2020. About 20% of adults and about 30% of children and adolescents are found to have sleep-disorders.

The following Figs. 3 – 5, illustrate the economic-burden of sleep-disorders.

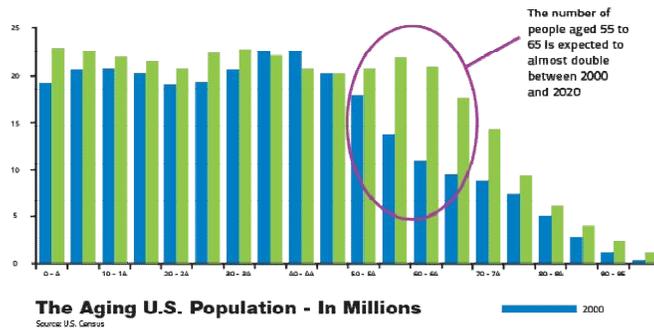


Fig. 2. The population of the US by Age-group, 2000 and 2020

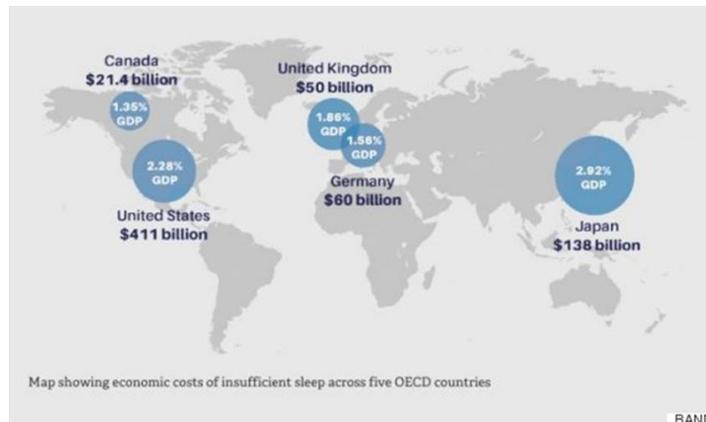


Fig. 3. Map showing economic costs of insufficient sleep across five OECD countries

	Costs (millions \$)
Substances used for insomnia	
Prescription medications	809.92
Nonprescription medications	325.80
Alcohol	780.39
Melatonin	50.00
<b>Total Cost of Substances</b>	<b>1,966.11</b>
Health care services for insomnia	
Outpatient physician visits	660.00
Psychologist visits	122.40
Social working visits	75.30
Sleep specialist visits	18.20
Mental health organizations	153.00
In-patient hospital care	30.80
Nursing home care	10,900.00
<b>Total</b>	<b>11,960.70</b>
<b>Total direct costs</b>	<b>13,926.11</b>

Fig. 4. Table showing the direct costs of insomnia in the US, 1995

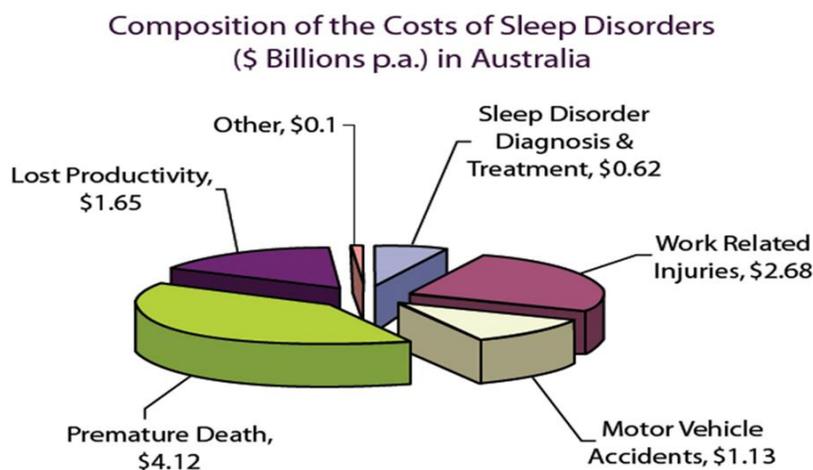


Fig. 5. The composition of the costs of sleep-disorders in Australia

In view of the morbidity, mortality, loss of Quality of Life, and Disease-burden including economic-cost of sleep-disorders, cost-effective Prevention Programs, touching upon Primary, Secondary and Tertiary Prevention need to be planned, implemented and evaluated. Such Programs need to educate parents, would-be parents, teachers and health-care professionals.

#### 4. CONCLUSION

The considerable amount of knowledge accumulated in recent times on the pediatric

aspects of sleep and its disorders remain under-utilized.

Health-education for parents and prospective-parents frequently pay little attention to sleep.

Medical-students and specialist-trainers including pediatricians and child-psychologist and teachers require better instruction/education since all these come in contact with many children and adolescents whose sleep is disturbed, sometimes with serious consequences. Doctors need to ask the patients additional questions

about sleep towards better accuracy of diagnosis.

Adolescents need to be taught and advised to sleep adequately and avoid extensive television-viewing and recreational computer-use.

The pattern of sleep-behaviors and disorders differs between children and adults. Some sleep-disorders previously thought to be seen mainly or exclusively in adults are now being recognized in children.

The cause of sleep-problems at any age are both physical and psychological possibilities (perhaps in combination). In children, as in adults, neurological, respiratory, metabolic, endocrine, genetic, medication, and additional physical factors can influence.

Parenting practices play a major part in many children's sleep-problems due to reasons that parental knowledge, attitudes, and emotional state frequently determine whether a child's sleep-pattern is a problem or not.

Whereas obesity is a common feature of obstructive sleep apnea (OSA) in adults, enlarged tonsils and adenoids are usually responsible in children. Although obesity is becoming an increasingly important factor at all ages, only a minority of children with OSA is overweight and indeed very early onset may cause low body weight from failure to thrive.

Adult OSA generally causes sleepiness and reduced activity. In contrast (as in other causes of excessive sleepiness such as narcolepsy), some sleepy children are abnormally active.

Since persistent sleep-disturbance can have harmful-outcome on mood, behavior, performance, social-function, and (sometimes) physical-health due to impaired concentration, memory, decision-making, and general ability to learn in addition to impaired motor-skill and impaired reaction-time such could have particularly serious-consequences in young-people. In addition to that, deficient-treatment (management) of childhood sleep-problems could persist in adult-life.

Treatment of most children's sleep-disorders is, in principle, straightforward and likely to be effective if appropriately selected and implemented with earnestness but many parents are unaware of frequently simple-ways in which sleep-problems in young children could be

prevented or minimized in the manner parents deal with children at bedtime or during the night.

Medication has a smaller part to play in children than it has in adults – behavioral-methods being found additionally appropriate and effective.

Since changes of behavior could result from sleep-disturbance, the affected-child's interpersonal-problems may extend beyond the family. Irritable, difficult, or disturbed-behavior could affect friendships and relationships with pedagogues could also suffer.

In view of these various potential-complications to the child's life everyone concerned must realize such could be at least partly be the result of sleep-disturbance to which effective-treatment exists in most instances.

In view of the morbidity, mortality, loss of Quality of Life, and Disease-burden including economic-cost of sleep-disorders, cost-effective Prevention Programs, touching upon Primary, Secondary and Tertiary Prevention need to be planned, implemented and evaluated. Such Programs need to educate parents, would-be parents, teachers and health-care professionals.

## CONSENT

It is not applicable.

## ETHICAL APPROVAL

It is not applicable.

## COMPETING INTERESTS

Authors have declared that no competing interests exist.

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