Sleep abnormalities in Pediatric CFS/ME

– A systematic review

Jennie Malene Eggesbø Steidel

University of Oslo
Faculty of Medicine
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Supervisor:
Vegard Bruun Bratholm Wyller

Abstract

Several studies have looked at sleep pathophysiology and perceived sleep in children and adolescents with CFS/ME, but they are difficult to compare due to varying case definitions, divergent methodology and in some cases poor reporting. In general, the studies find that CFS/ME patients suffer from disturbed sleep using subjective measures. However, the use of objective measures of sleep quality have been less consistent, often failing to confirm the subjective reports of impaired sleep quality. The later studies indicate that perception of sleep is an important factor. A few studies included measures of depression and anxiety and found that they were determinants of poor sleep in CFS/ME. Thus, the awareness and treatment of common comorbidities to CFS/ME are important. Studies also need to distinguish between actual sleep quality and the perception of sleep quality. Future studies should include patients based on an international standard case definition, preferably clinician verified, follow up patients over time and take into account comorbidities. More research is needed, but a positive trend towards better studies gives hope of future concrete evidence to inform future treatments of sleep disturbances in CFS/ME patients in the clinical setting.

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Definitions and Abbreviations

CFS and CFS/ME: Chronic Fatigue Syndrome/Myalgic Encephalomyelitis. The lack of a clear definition has resulted in both names (discussed under 'Background'), in this article both abbreviations are thus in use. When referencing an article the corresponding normative is kept.

Sleep quality: is defined as one's satisfaction of the sleep experience, integrating aspects of sleep initiation, sleep maintenance, sleep quantity, and refreshment upon awakening.

Actigraph: a small device usually worn on the wrist that records the activity level of the body by sensing physical movement and that is used especially to measure the amount and quality of sleep

Actigraphy: an objective test that is useful in identifying sleep-state misperception, sleep-interruption insomnia, and circadian rhythm disorders

Sleep Onset Latency, **SOL** %: time from bedtime to onset of sleep, also called sleep latency

Sleep Efficiency, **SE** %: ratio of total sleep time (TST) to time in bed (TIB), where time in bed excludes non-sleep related activities but includes the amount of time spent attempting to initially fall asleep and time out of bed during nighttime awakenings, a manifestation of sleep discontinuity

Time in bed, **TIB** (min): total time spent in bed

Total sleep time, **TST** (min): total time spent sleeping

BT: Bet time

RT: Rise time

Very short sleep **VSS**: VSS index gives the percentage of sleep less than 180 minutes (3 hours) of total sleep time. When it is high, it means that the subject has disrupted sleep.

Day time activity index **DTA**: shows a circadian rhythm of activity. When a subject is active during the day and can rest at night, the DTA index is high. When a subject has a reversed day/night rhythm, the DTA index is below 1. Subjects with a disturbed circadian rhythm have a DTA index around 1. It is based upon average epochs during the day (from 8 a.m. to 9 p.m.)/average epochs at night (from midnight to 5 a.m.)

Wake after sleep onset, **WASO** %: Percentage of time spent awake after first onset of sleep. By excluding the wakefulness occurring before sleep onset, it gives a reflection of sleep fragmentation.

REM sleep: Rapid eye movement sleep (REM sleep or REMS) is a sleep phase characterized by random rapid movement of the eyes, accompanied by low muscle tone throughout the body, and the propensity of the sleeper to dream vividly.

REM sleep latency: interval from sleep onset to first appearance of REM sleep

NREM sleep: NREM (non-rapid eye movement) sleep is dreamless sleep. During NREM, the brain waves on the electroencephalographic (EEG) recording are typically slow and of high voltage, the breathing and heart rate are slow and regular, the blood pressure is low, and the sleeper is relatively still. NREM sleep is divided into stages 1, 2, 3, and 4, representing a continuum of relative depth. Each has unique characteristics including variations in brain wave patterns, eye movements, and muscle tone.

NREM stage 1: Transitional phase that occurs between wakefulness and sleep, the period during which we drift off to sleep. During this time, there is a slowdown in both the rates of respiration and heartbeat.

NREM stage 2: You become less aware of your surroundings. Body temperature drops. Breathing and heart rate become more regular. Lasts for approximately 20 minutes

NREM stage 3+4. The deepest phases of NREM sleep, and is characterized by delta waves (measured by EEG) which are very slow brain waves. It's hard for someone to wake you up during this stage. You have no eye movement or muscle activity

Slow-wave sleep **SWS**: Dreaming and sleepwalking can occur during SWS. SWS is thought to be important for memory consolidation.

Polysomnography **PSG** (sleep study): a comprehensive test used to diagnose sleep disorders. Polysomnography records the patient's brain waves, the oxygen level in blood, heart rate and breathing, as well as eye and leg movements during the study.

Electroencephalography (**EEG**): recording of the brain's spontaneous electrical activity over a period of time, as recorded from multiple electrodes placed on the scalp, part of PSG

Electrooculography (**EOG**): eye electrodes that allow monitoring of the slow, rolling eye movements commonly associated with sleep onset and the rapid eye movements of REM sleep, part of PSG

Electromyography (**EMG**): electrodes to measure muscle tension and movement in the body, often placed on chin and leg, part of PSG

Electrocardiography (**ECG**): determines heart activity by measuring signals from electrodes placed on the torso, arms and legs, used by PSG

HRV: heart rate variability

Arousal: is an abrupt change in the pattern of brain wave activity, as measured by an EEG. Arousal typically represents a shift from deep sleep to light sleep, or from sleep to wakefulness.

Insomnia: a term generally used to describe difficulties falling asleep or staying asleep and is more specifically defined in diagnostic manuals as difficulty initiating or maintaining sleep, or having non-restorative sleep despite having adequate opportunity for sleep that interferes significantly with functioning

HPA axis: hypothalamus-pituitary-adrenal axis is a complex set of direct influences and feedback interactions among three components: the hypothalamus, the pituitary gland, and the adrenal glands

GP: General Practitioner

DAGs: drawing and analyzing causal diagrams

OSA: Obstructive Sleep Apnea

INTRODUCTION

CFS/ME is a debilitating illness with still a lot of unknowns. Sleep abnormalities and unrefreshed sleep is a hallmark of CFS/ME. This is well documented in adults, but less research has been done to clarify this aspect in the children and adolescent patient population. More attention towards this field is much needed in this group given the importance of sleep during development. However, it is a challenge to study due to the complexity of distinguishing between normal sleep patterns and disturbed patterns. This is especially true in adolescents, the age when CFS/ME commonly has its onset [1]. This study aims to summarize current knowledge on occurrence and characteristics of sleep disturbances in pediatric CFS/ME.

CFS/ME description

The syndrome is characterized by disabling fatigue over 6 months (in some pediatric definitions less) which cannot be explained by any other known condition, including major depression, coupled with post-exertional malaise, joint pain, headaches, sore throat, adenopathy, diffuse myalgia, orthostatic intolerance and cognitive difficulties such as impaired memory and lack of concentration and the ability to focus. Despite extensive research on adult CFS there is no clear understanding of the pathophysiology or etiology of the disease and there is much debate surrounding the case definition as well as the potential treatment for this group. As of today several therapies have been tested, but there have often been limitations in the studies and conflicting results have been published [2]. The current management of the disease, according to most guidelines, is therefore reduced to symptom management.

Sleep disturbances are widely reported in this population and are considered a cardinal symptom of CFS. Most definitions specify disturbed or unrefreshing sleep as one of several typical symptoms, and it has been recorded among 95–97% of adult and adolescent patients [3, 4] and in 85% of the pediatric patients under 12 years of age [3]. Both the quantity of sleep and sleep rhythm can be altered and include hypersomnia during the day and insomnia during the night [5].

Prevalence

The prevalence of pediatric CFS/ME is estimated to be between 0.001% to 5 %, although estimates differ widely across studies [6-8]. Although CFS is rare, fatigue is not. In one study the prevalence of fatigue was three times more common than CSF [8] and it is a common complaint in the GP's office [9].

CFS in pediatric cases usually have its onset in the mid to late teens and the estimated prevalence of CFS/ME in this age group has been estimated to be between 0.1–1.29% [10-14]. However, the lack of unambiguous criteria for CSF hinders accurate prevalence data in both children and adults [15].

The severity of disease is usually not noted in studies, and the prevalence of severe CSF is not yet known [16, 17]. The heterogeneity of the patient group and large variation in degree of severity may in part explain the varying prevalence estimates of CFS/ME, and why research results may give conflicting results. Few longitudinal studies have been published, restricting our knowledge of the natural course of the disease and its prognosis. Yet, it seems clear that the prognosis is better for pediatric CFS/ME than for adult CSF/ME [18]. While the percentage of women diagnosed with ME/CFS is higher than the percentage of men, ME/CFS is not a "women's disease". Thirty-five to forty percent of diagnosed patients are men [19].

CFS/ME Background

Several clusters of symptoms similar to what we today call CFS/ME have been noticed for centuries. This is described by Jackson and Bruck [20] in their review of sleep abnormalities in adult CFS/ME from 2012 and the review from Rivera et al. in 2019 [21]. These clusters included symptoms such as fatigue, pain, sleep disruption in addition to cognitive and mood changes. The first mentions of clusters that were more specific to CFS/ME date back to the 19th century [22]. The term "neurasthenia" was set in 1869 to describe this collection of symptoms and was widely used. As psychiatric disorders became more defined and evidence-based, the use of the term diminished.

In 1969 the term ME 'myalgic encephalomyelitis' was included in WHO's International Classification of Diseases. It came into use after seeing over time a rise in post-infection cases, some of them becoming endemic. Patients typically suffered from a benign flu-like symptom cluster and early investigations found evidence of encephalomyelitis. The renaming of the term, to 'myalgia nervosa', was proposed by the European Psychiatric Society in 1970 limiting the research efforts to other fields for some time [23].

It also became entwined with post infectious mononucleosis syndrome. Later it was established that they were uniquely different entities, after research identified cases without a clear infectious beginning and cases triggered by traumatic events. In 1988 the American CDC (Center for Disease Control and Prevention) had an expert panel review the current evidence and suggested the term "chronic fatigue syndrome", CFS, since this was the most common characteristic/complaint. ME was more widely in use at that point, and this gave rise to the term CFS/ME.

The development of a case definition allows for a systematic and comprehensive approach to defining the etiology and pathophysiology. However, through the years of research and clinical investigations, more than 20 different case definitions have been proposed (up till the year 2013) [24]. The earliest case definition was established by CDC in 1988, and also the Australian case definitions and the Oxford case definition [25] were early. These initial definitions have been criticized, and although they were seen as strict, the criteria did not exclude sleep disorders.

In 1994 the Fukuda case definition for research was established by the American CDC. CFS/ME was seen as a diagnosis of exclusion, so the new criteria specifically excluded comorbid conditions such as primary sleep disorders like obstructive sleep apnea and narcolepsy, as well as other potential causes of fatigue. It is today the most commonly used definition in clinical trials, even though it has later been criticized for being too wide, and may encompass other conditions such as depressive disorders.

In 2003 an international expert panel developed clinical guidelines for healthcare professionals, later called the Canada criteria. They included more categories of potential symptoms and are considered "stricter" as more symptoms are required to fulfill the criteria. Sleep disturbances in the Canada criteria is recognized as a major feature. It included sleep and circadian rhythms disturbances such

as insomnia, reversed or abnormal diurnal and sleep rhythms, while it excluded treatable sleep disorders.

In 2012 the Canada criteria was used as a basis for the development of the ICC, the International Consensus Criteria, which identified distinct clusters of symptoms as diagnostics for CFS/ME. The aim of the ICC was to simplify setting a diagnosis in a clinical setting in addition to assist in finding patients for research studies.

Several attempts have been made to make a pediatric definition, meanwhile the case definitions for adult CFS/ME is being used in research on pediatric cases as well. Reeves et al. in 2003 published a case definition modified from the 1994 Fukuda criteria, but this was not based on research on the pediatric population [26]. In 2006, the International Association of Chronic Fatigue Syndrome Pediatric Case Definition Working group published a CFS/ME pediatric case definition. It aspired to make research on pediatric CFS/ME more uniform, but it has not been universally accepted and many research groups have opted to use other, more widely recognized definitions instead.

In one of the studies relevant to this article, Loades et al. [1], they use an internal British guidance document produced by the National Institute of Clinical Excellence (NICE) in 2007. This document was rewritten in 2020 with major changes, and the proposed update has provoked a highly polarized response. Changes in the guidance include recommendations to perform interventions as early as 12 weeks after onset of symptoms. It also contains new recommendations related to exercise. NICE uses the GRADE system, which sets out a series of isolated questions using the PICO (patient, intervention, comparison, and outcome) framework and then rates the quality of research evidence for each recommendation. Within the hierarchy, evidence from randomized trials starts high, but is downgraded if trials fail to meet strict quality criteria.

CFS/ME impact on pediatric patients

Chronic fatigue results in a significant functional disability and frequently has large consequences on an individual's career opportunities, social life and general quality of life. Adolescents and children are likely more vulnerable than adults as they are affected at a stage in life where they are exploring the self and it can have repercussions for sexuality, self-image, self-perception, self-confidence and social interactions. Studies have also shown that low physical functioning, caused by pain and fatigue, in CFS in children up to 18 years lead to low school attendance [27]. In fact this is so common that some even require this as a criteria for disease (functional disability). This affects learning, grades, education and thereby future career opportunities. Reduced school attendance may also have consequences for the social network and opportunity to make and keep friends.

CFS/ME and sleep research

CFS/ME has long been in research focus among adults, and only recently recognized as a pediatric condition as well. The diagnosis of CFS/ME is increasingly gaining more attention in this population.

From studies conducted in adults we know that CFS patients experience disturbances in sleep. In a recent study by Tobback et al. on adult CFS patients, they found that they have a longer sleep latency and more awakenings and less sleep quality [28]. In 2012 a thorough review of sleep abnormalities [20] in adult CFS patients was done, covering a large amount of literature, but there were few consistent findings and it highlighted the need for more research. However, an interesting observation were the noted discrepancies between objective measures of sleep and subjectively reports. In addition, some indications of altered cortisol levels and heart rate variations were

included as possible underlying mechanisms of an altered sleep architecture, with differences in sleep stage transitions and instability.

A review of sleep disturbances in pediatric CFS/ME was conducted by Snodgrass et al. [29] in 2015. They only managed to identify 6 studies on the subject and concluded that a great deal of research was required to really understand the intricate connection between CFS/ME and sleep. They found that similar to the findings in adult research, children also suffered from subjective sleep disturbances, while more varied results were found when looking at objective measures of sleep. They concluded that there is inadequate evidence to ascertain what type and severity of sleep disturbance these patients suffer from, that little research has been done on possible factors pertaining to sleep in the pediatric population and that to date there are no treatment trials which support general or specific sleep interventions in this young CFS/ME group [29]. The review stated that studies cited were difficult to compare due to varying methods for assessing sleep and the use of divergent criteria for CFS. The results of each study and the applicability to general CFS populations were also questioned due to small sample sizes and underreported background information on the participants.

This review aims to summarize current research and specifically focus on any new studies that may have addressed the concerns, or filled in any gaps, in the field as outlined by Snodgrass et al. [29]. An update on this field could help guide future sleep research in addition to aid authorities and health care professionals in making decisions on CFS treatment.

Role of sleep in children and adolescents

The important role of sleep on the development and maturation of the child brain is well documented. Sufficient amount and quality of sleep reduces the risk of developing a psychiatric disorder later [30-33], and helps regulate mood and anxiety. Sleep difficulties are known to be associated with depression and anxiety and the prevalence of depression and anxiety is particularly high in adolescents with CFS [34]. Finally, decreased subjective sleep quality limits their activity, assessed objectively using actigraphy [35].

Obtaining the optimal amount of sleep has been linked to improved concentration and attention [36] and better functioning across a range of outcomes [37]. The brain processes memory and experiences during sleep and is crucial for learning. Disruption of normal sleep patterns in children and adolescents with CFS is therefore a critical aspect of the disease and has a vital effect on the performance and daily life of the youth.

The body clock mechanism is based on 24-hour rhythms of sleep and wakefulness. It utilizes information about the surroundings from the photoreceptors in the eyes, and uses the sleep pressure which builds up while awake, to regulate sleep [38]. Adolescents' daily routines, such as mealtimes and regular activities like getting dressed and being engaged in activity during the day, are altered extensively with the onset of CFS/ME. Disruption in the daily routines may affect the body clock rhythm [39].

Normal sleep patterns are not uniform across the pediatric age group. Sleep requirements change from sleeping nearly all day as an infant to sleeping less and social jetlag during adolescence, which as mentioned is the age when most pediatric cases of CFS have their onset. Teenage sleeping habits are often distinct from smaller children or adults and some can be detrimental to sleep quality. Factors such as social media, video games, the use of smartphones, fear of missing out (FOMO) culture, and an exploding online community seem to have drawn teenagers to sleep less and less over the last decade. Screen usage is associated with shortened sleep duration and delayed sleep

onset [40, 41], and this sleep disturbance may contribute to developing symptoms of depression [42]. Adolescents may consume caffeine or energy drinks as an attempt to overcome fatigue [43], which may further contribute to altering sleep patterns, although this has not been explicitly investigated in adolescents with CFS.

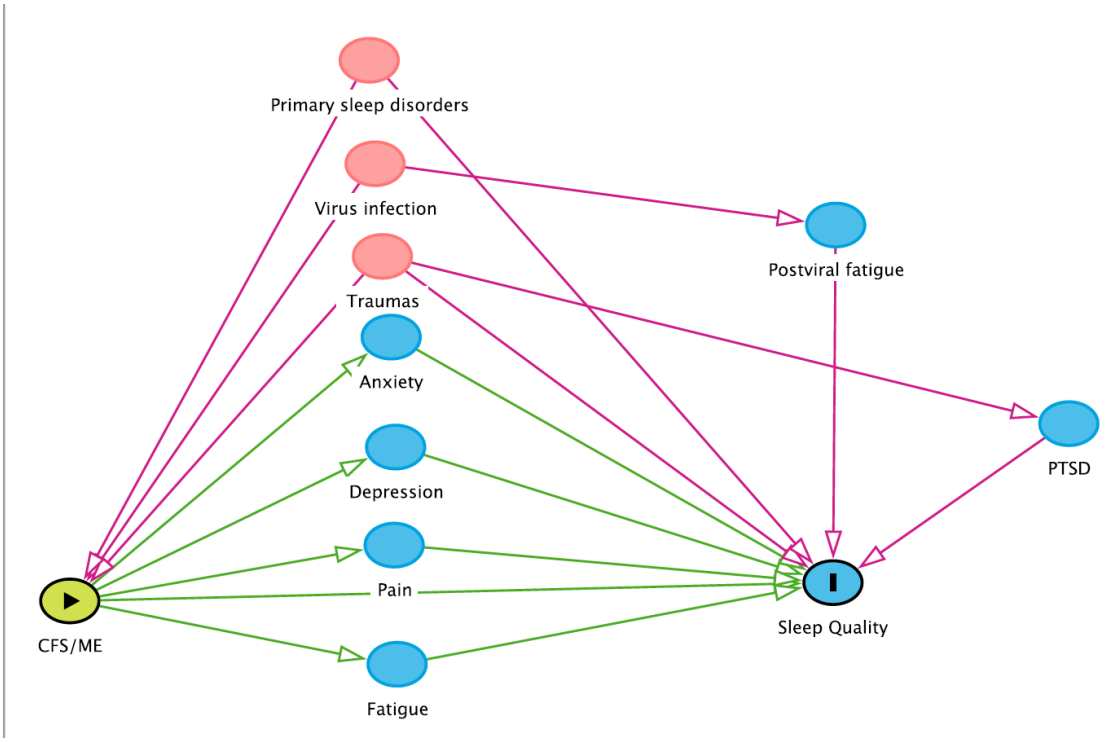
In the unexpected finding of how preadolescents do not respond to noise stimuli, as high as up to 90dB above waking threshold values, when sleeping (sleep stage 1 and to some extent in other sleep stages) [44], suggest that the brain may not be fully developed in this aspect or it may be a protective factor for an important sleep-related function to occur. They further acknowledge that many important processes take place while sleeping (such as maturation and restoration of physiologic and neurochemical processes) and that these processes are more intense during childhood. Sleep disruption with awakenings or even arousals may thus be a greater concern for adolescents than for adult CFS patients, as uninterrupted sleep probably is a prerequisite for these processes to run optimally.

Adolescents exhibit a delayed circadian rhythm, making it more natural for adolescents to go to bed later than children and adults [45-47]. These changes in sleep patterns in adolescents are more than a mere change in habits and can be explained in part by changes in the neurobiological regulation of sleep[48]. It also brings reduced total sleep time, longer sleep onset latency, and less rapid eye movement (REM) sleep [45, 46, 49]. This delayed circadian rhythm in adolescents often results in sleep deprivation during the weekdays, from which they try to recover in the weekend, this phenomenon is also called 'social jetlag' [50, 51]. Overall, it is necessary to keep in mind the profound changes in hormones and physiology in prepubertal and pubertal children, and distinguish if any specific alterations may stem from natural changes in this period in life, or from CFS.

Factors related to sleep in CFS/ME patients

The associations between CFS/ME and sleep are complex and involve many pathways. CFS/ME has several aspects of the disease that might contribute, exacerbate or play a role in the continuation of the sleep disturbances reported. It is a challenge to discern whether sleep disturbances may be part of the causal factors of the disease, are a consequence of the underlying pathophysiology, or may be a consequence of other symptoms related to CFS. A model of the complex interplay that could exist between some factors, either directly or indirectly related to sleep problems in CFS/ME patients, is shown in DAG, Fig 1.

Figure 1, DAG causal factors of sleep and CFS/ME;  ancestor of outcome,  ancestor of exposure *and* outcome



The following chapters discuss some of the conditions that CFS/ME increases the risk of suffering from, which may then again affect sleep (factors colored blue in the figure).

Anxiety and sleep

Anxiety is prevalent in the young CFS population. Knight and colleagues found that 17% of adolescents with CFS/ME in their study had comorbid anxiety based on a retrospective review of medical records. Higher rates are found when based on diagnostic interviews and self-reported questionnaires, where estimates as high as 50% emerge [52].

Several studies have looked at the effect of anxiety on sleep. An association between subjective presleep rumination and objective sleep onset latency has been reported [53], indicating that sleep may be affected in individuals with symptoms of anxiety. One aspect of anxiety may be so-called 'catastrophizing' thoughts. Some have found that this trait is quite common in adolescents with CFS [54] and it has been associated with sleep disturbances [55, 56].

However, it's likely a bidirectional effect, as extensive research has documented that sleep problems can lead to anxiety and depression [30-33]. It may also be that the profound impact of CFS on functioning, uncertainty tied to prognosis and diagnosis, and other aspects of CFS/ME, likely affects mood and increases risk of anxiety and depression [57].

It is critical that psychological factors such as anxiety are measured in a standardized manner, in order to understand the specific contribution of anxiety to sleep disturbances in CSF/ME.

Depression and sleep

One third of children with CFS/ME seen in specialist services in the UK have comorbid depression, however it is not yet known whether depression increases risk of CFS/ME or is secondary to the disease [58].

It is well documented that sleep difficulties contribute to depression [32, 59], and that depression also affects sleep quality, thus a bidirectional relationship is generally acknowledged [43]. Treating depression and anxiety, which is common in adolescents with CFS [34], may therefore be important to prioritize. Sleep disturbance is a common symptom of psychiatric conditions [60] which may support that sleep disturbance in CFS/ME could be a secondary consequence of comorbid depression. It may be that the emotional distress, and low mood tied to CFS may lead to disrupted sleep over time [57]. Studies that have explored this potential link by comparing results of CFS/ME patients with and without a psychiatric comorbidity suggest that sleep disturbances are common in both subtypes, and therefore do not appear to be solely the result of underlying depression[61, 62].

A recent adult CFS study found that subjectively experienced sleep disruption was associated with fatigue [63]. Interestingly, objective measures of sleep difficulties were not associated with fatigue. Also scoring conducted in the morning found that low mood may affect the connection between fatigue and subjectively experienced sleep.

Pain and sleep

A common feature of CFS/ME is generalized joint pain and myalgia. Other comorbidities are also associated with these symptoms, such as irritable bowel syndrome and migraine. In general, chronic pain is commonly associated with sleep problems and is also a predictor of impaired quality of life over time [64, 65]. Not much research has been done on the influence of myalgic symptoms on sleep disturbance in CFS/ME.

CFS/ME patients report more awakenings caused by pain, when compared to depressed patients [62]. Several studies on patients with fibromyalgia have shown that pain sensitivity is associated with poorer subjective sleep, as well as objective measures of sleep disturbances such as less REM sleep and more SWS [66 67]. Increased alpha and decreased delta activity recordings on sleep EEG, with the results of decreased sleep quality, was a result after an experiment where muscles during sleep were given pain stimuli [68, 69].

A potential bidirectional relationship exists between sleep and pain. Experiencing pain has proved to disrupt sleep by making it hard to initiate sleep and changing sleep patterns, and poor sleep can cause increased pain perception by altering pain sensitivity [70]. By disrupting slow wave sleep, symptoms of pain and fatigue have been induced in otherwise healthy individuals [70].

Fatigue and sleep

Fatigue is a common complaint at the GP's office, while CFS/ME is a rare disease. Many of the cases presenting as fatigue in the GP's office are caused by sleep disorders, mood disorders, or reactions to an overload situation or from experiencing strong grief. Still fatigue plays a central role in CFS/ME as the name CFS suggests.

The effect of fatigue on sleep in children and adolescents with CFS/ME has been given little attention. Fatigue leads to reduced or limited daytime activity, which in turn may lead to inadequate buildup of sleep pressure, causing difficulties in falling asleep. Poor sleep may in turn cause fatigue or sleepiness during the day, mood disturbances and exacerbate other symptoms such as anxiety. This easily becomes a self-reinforcing cycle.

Sleep disorders

There are also other potential etiological factors, which may impact sleep. Some studies have found high percentages of sleep disorders in CFS patients. In one study by Fossey et al. over 50% of the CFS participants had a clinical sleep disorder when investigated [71]. Le bon et al. followed this up with a study which found that using MSLT, 30% of the CFS patients were clinically sleepy [72]. This is important as sleepiness is more closely associated with primary sleep disorders than CFS/ME, which is associated with fatigue. The difference is clinically difficult to separate and the authors concluded that the patients suffering from sleep disorders could not be distinguished from the CFS patients based on presenting symptoms.

As a result of such studies many have speculated if a proportion of the CFS patients actually stem from a sleep disorder such as OSA, narcolepsy or periodic limb movement disorder. Repetitive limb movement during sleep is recognized to cause impaired sleep due to frequent arousals, but when analyzed for CFS patients there have been conflicting findings [73]. However, as perceived and objective measure of sleepiness has been found to not correlate with perceived fatigue, several authors have suggested that CFS is a separate disease and that primary sleep disorders may represent a comorbidity in CFS/ME patients.

Infection and Trauma

Viral infections have been known to cause other CFS-like syndromes such as Post viral fatigue syndrome. This is often associated with mononucleosis. Trauma has also been cited as a possible trigger of CFS/ME. Traumatic experiences may also trigger PTSD in some subjects and this may be characterized by nightmares and insomnia, 70-91% of PTSD patients reported difficulty falling or staying asleep in a study by Mahler et al [74].

Summary

CFS is a complex and multifaceted disease which represents a challenge when researching specific aspects, such as sleep. One of the issues of studying sleep disturbances in this patient group is the unknown directional relationship between the potentially pathological findings. Sleep disturbances in this population offer itself as a target for treatment, and whether primary or secondary, an improvement of sleep may be expected to improve many CFS/ME symptoms and comorbidities such as anxiety, fatigue and pain.

The DAG model, presented in Figure 2, is probably a closer approximation. As apparent from Figure 2, a significant portion of the variables are here not so easily classified as one or the other because of interconnectivity.

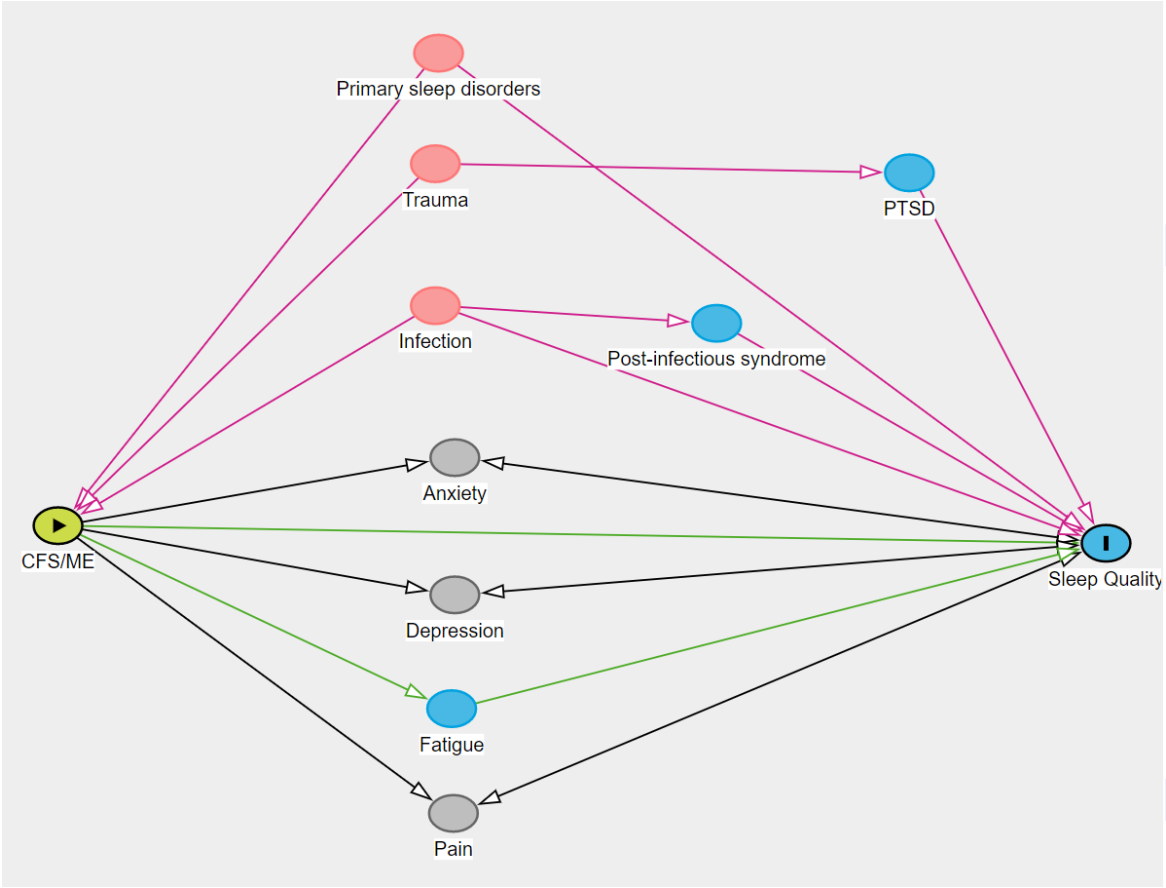


Figure 2, DAG causal factors of sleep and CFS/ME; ancestor of outcome, ancestor of exposure *and* outcome, other variable

Sleep assessment tools

Several different methods for assessing sleep have been used. Each method has different strengths and weaknesses and in many cases the feasibility of a method is dependent on the number of participants, study layout or other deciding factors such as costs. Larger studies are more costly and therefore it is important to select a method which is both feasible and not too costly, whereas more extensive mapping can be done in a smaller study which can be hypothesis generating.

An extensive method to assess sleep, couples subjective and objective measures. Early research held high hopes for bio-markers related to sleep, but that avenue has failed to produce any consistent results. Subjective measures such as sleep/wake diaries or sleep quality questionnaires, can be verified using either polysomnography or actigraphy, as described below.

Several of the studies analyzed in this review used both subjective and objective measures for sleep, often verifying or coupling the two modalities (eg. using a sleep/wake diary with actigraphy). Looking at both can be valuable as Josev et al. [75] explained, since the results can be used to shape diagnostics in the future. Should the findings find high correlation between subjective and objective sleep measurements then the clinicians can safely use subjective screening tools which are significantly cheaper than objective testing. Should the results not correlate then that might suggest different management of CFS patients in the future.

Polysomnography

Polysomnography [76] is the gold standard for diagnosing sleep-related disorders and is also used extensively in sleep research. The procedure collects physiologic parameters during overnight sleep in a sleep studio, where the patient is attached to numerous equipment. EEG recording of the brain activity together with EOG recording of eye movements, ERG measuring the retina of the eye and EMG measurements gives an objective assessment of sleep that lets you look at sleep architecture and sleep staging. Typical information obtained are sleep onset latency, the REM-sleep onset latency, total sleep duration, percentage and duration of every sleep stage, the number of awakening during the sleep period, and the number of arousals.

Recently PSG for use at home has been introduced, and it has many advantages. Besides the obvious expense reduction, it is possible that first-night effects may influence the results in patients who do not have a primary sleep disorder [77]. This may manifest as less TST and lower SE, due to the initial apprehension of being "under observation" or feeling uncomfortable with the multiple electrodes and cables used.

Although when at home, the relatively nonstandardized nature of home recordings, where there are more extraneous influences that could affect the results, it would be assumed that sleep at home will be less consolidated [73]. This is apparently not the case as seen from a recent comparison between home and laboratory norms [78], and there is also consistently demonstrated absence of significant first night effects in home recordings[79, 80] in contrast to what is the case in the unfamiliar laboratory setting. So it is beneficial and more valid results can be obtained by observing the sleep pattern of children sleeping in their own beds [73].

Some sophisticated home study devices have most of the monitoring capability of their sleep lab technician run counterparts [81]. With home PSG the patient can apply the screening device for one to several days, before returning the device. Several days would produce a more consolidated sleep assessment, but the more sophisticated home study devices can be complex and time-consuming to set up for self-monitoring.

Until very recently, a disadvantage was a lack of normative data for home PSG on patients of any age, but Stores and colleagues [78] have compiled such norms for children aged 5–16 years.

Actigraphy

Actigraphy does not specifically document sleep, but movement and position. Usually it is a band to tie on the body that contains a gyroscope which can measure activity level and posture of the body during the night and the day.

It is an objective measure of sleep, but has some drawbacks. It is less likely to focus on shorter periods of sleep for patients with fragmented sleep. There is no measure of sleep efficiency and it has been shown that it overestimates sleep when the participants could just be lying still in bed [82]. Actigraphy is thus less accurate, but cheaper, and can easily be worn for several days to find an average. Another benefit is that it can be used at home in a familiar environment which better simulates regular sleep for the participant. Josev et al. [75] emphasizes this also, seeing that the measure of sleep quality became more valid and sensitive, being done in the naturalistic setting of the patients own home, unfortunately the use of actigraphy in pediatric CFS/ME studies is relatively rare [20, 83].

The device gyroscope defines a horizontal line called Zero and measures position based on when this line is crossed. This is called the Zero-cross method. It can then calculate UP and DOWN time and use algorithms to calculate sleep and wake periods. The choice and quality of the algorithm is crucial

to the outcome [84]. When the actigraphy includes an accelerometer giving the linear acceleration of movement, it has also shown reliable results for measuring sleep–wake rhythm [85] and can record objective activity levels.

Actigraphy coupled with a sleep-wake diary, may improve the outcome. Josev et al. [75] did this and included light exposure in the actigraphy as well. He also used visual screening instead of automated algorithms when assessing the recordings [86].

To thoroughly assess sleep quality there is a need to collect more data than an actigraph is capable of, such as measurement of sleep stages, arousal, and abnormal movements. As mentioned, the assumption that onset and maintenance of sleep is determined by absence of movements recorded, may underestimate not just night wakings but sleep onset in patients that are lying still but awake, not uncommon in CFS.

Subjective tools

Subjective measures are important because they are often a more economically and methodologically feasible way of measuring sleep quality [87]. They provide valuable information about the patient's sleep experience which has the potential to influence objective measurements.

Sleep questionnaires will try to systematically capture sleep parameters from patients for analysis. Several different types have been validated for adolescents, tailored to different needs, but typically they ask questions about when they went to bed, when they fell asleep, number of awakening and perception of sleep quality. Some include questions about day-time naps and the amount of daytime activity. The questionnaires are cheap and can be sent out several times during the research period. This gives comparable data to analyze. They are however they are subjective and studies have found them to differ from objective findings in several cases. There is no consensus on which one is superior in research using children and adolescents. The questionnaires can also overestimate sleep in cases where the sleep pattern is very variable from day to day, with an unstable sleep rhythm.

Sleep-wake diaries have mainly been used to log sleep. It is less accurate than for example actigraphy, but it is commonly used to assess sleep disturbances in a GP setting. It can illuminate a certain pattern and highlight differences between weekends and weekdays, and be used over several weeks to assess the effect of treatment. However, being subjective it will never be accurate. For example a person with insomnia will often overestimate the time it takes to fall asleep.

The nature of the disease CFS/ME with its cognitive impairment (both awareness, recollection, and the lack of energy to accurately and consistently perform a diary chore) together with sleep abnormalities, might make the subjective tools less suitable than for the population in general.

Biological measures

There are some biological measures used in sleep assessments. Blood sample testing will find the levels of the sleep hormone Melatonin and the activating hormone Cortisol. These hormones vary in patterns throughout the day and night and disturbances in these systems can identify some pathophysiology. But the methods are often inaccurate because of test variation and many factors can influence the level of these hormones. Additionally the tests are costly to analyze. This makes them less available in general and less likely to be used in large scale studies.

Melatonin abnormalities have been seen in other sleep related disorders that are characterized with unrefreshed sleep, such as for patients with delayed-sleep-syndrome. Their levels are normal but the nocturnal rise of melatonin is delayed compared to controls. It has been suggested that the sleep

problems CFS patients are reporting may be due to abnormal melatonin as well, expecting insufficient melatonin levels, but Knook et al. [88] measurements surprisingly showed elevated levels.

Fibromyalgia adult patients with sleep problems have shown lower melatonin levels at night [89], however Korszun et al. results [90] showed elevated plasma melatonin when examining adult women with fibromyalgia, interestingly the same study showed no abnormalities for the adult CFS group.

Patients with hypothalamic amenorrhea have been found to have increased melatonin levels. This syndrome is associated with dysregulation of the HPA axis [91]. The neuroendocrine HPA axis controls reaction to stress and is involved in the regulation of important processes that are relevant to many CFS symptoms, such as energy storage and expenditure, the immune system and mood/emotions. There are many theories connecting CFS patients with HPA axis distortion and autonomic nerve system dysfunction due to the substantial research of the pathophysiology of CFS/ME indicating that the HPA axis may be implicated [92, 93]. As of now, there is no evidence that this axis is disturbed in adolescents with CFS [94].

There are also suggestions that a dysfunctional regulation of the core body temperature may be a reason why we see sleep problems in CFS patients. Body temperature and cortisol is kept stable and high during the day, then lowered by 1-2 degrees during the night [95] with a gradual decrease that coincides with sleepiness before bedtime and melatonin release, but there are large natural variances for each individual.

The heart rate variability is in CFS/ME patients found to be significantly lower, compared to controls, indicating a reduction in nightly parasympathetic activity [96-99]. That the HRV is decreased implicates a persistent state of automatic hypervigilance in these patients, however the lower daytime physical activity might be a confounding factor. In one study it was demonstrated that HRV was the best predictor for how the CFS/ME patients perceived their subjective sleep quality [96]. There might be some who are more susceptible to becoming ill with CFS/ME due to a heredity altered physiological mechanism [100].

METHODS

Protocol

The systematic review was conducted according to the PRISMA 2009 statement (Preferred Reporting Items for Systematic Reviews and Meta-Analyses [101]. We tried to assess the studies through the STROBE statement (STrengthening the Reporting of OBservational studies in Epidemiology) [102] as previously attempted by the last systematic review which reviewed articles published between 1987 and 2014 [29].

Eligibility criteria

The Eligibility criteria for this study was any human study in PubMed which primary assessed sleep disturbances in children and adolescents from the age of 0 to 18 which have received the diagnose chronic fatigue syndrome (CFS) or myalgic encephalomyelitis (ME) and reported empirical data. It was decided to include everyone regardless of which definition of CFS/ME was used to make the diagnosis as no one definition is considered superior worldwide and various definitions have been used. Furthermore including all definitions of CFS/ME allowed us to sample a larger pool of articles of which there already are few. In addition to these criteria the articles had to be published in English, had to be peer reviewed and needed to be published after 1987, the year when the CFS

diagnosis was officially first launched. We excluded conference papers, opinions/letters and qualitative studies.

We also excluded studies which looked at other conditions/populations in which chronic fatigue is a prominent symptom such as Morbus Crohn's disease, multiple sclerosis, and patients with major depression and cancer survivors. Many of these conditions have to be excluded as a cause of the fatigue the child or adolescent is experiencing, but not all definitions completely exclude patients with coexisting psychiatric disorders such as anxiety and mild to moderate depression. It was a debate whether or not to exclude all studies which included patients who had scored or reported symptoms conclusive of depression or other psychiatric illnesses since the diagnosis could possibly, at least partially, explain some of the symptoms experienced, especially sleep disturbances. In the end we decided to include these studies as well and trust that the CFS/ME diagnosis was made accurately, excluding any other plausible cause. It is also difficult to know if these symptoms are causational or debuted as a reaction to living with an invisible chronic disease with an unknown cause and which has been stigmatized by healthcare workers and the community.

Inclusion criteria:

- Aim to assess sleep problems/disturbances in pediatric CFS/ME
- Reporting empirical data
- Age ≤ 18 years
- In English
- Peer reviewed

Exclusion criteria:

- Conference papers
- Other conditions/populations (MS, depression etc)
- Opinions, Letters, etc.
- Qualitative studies

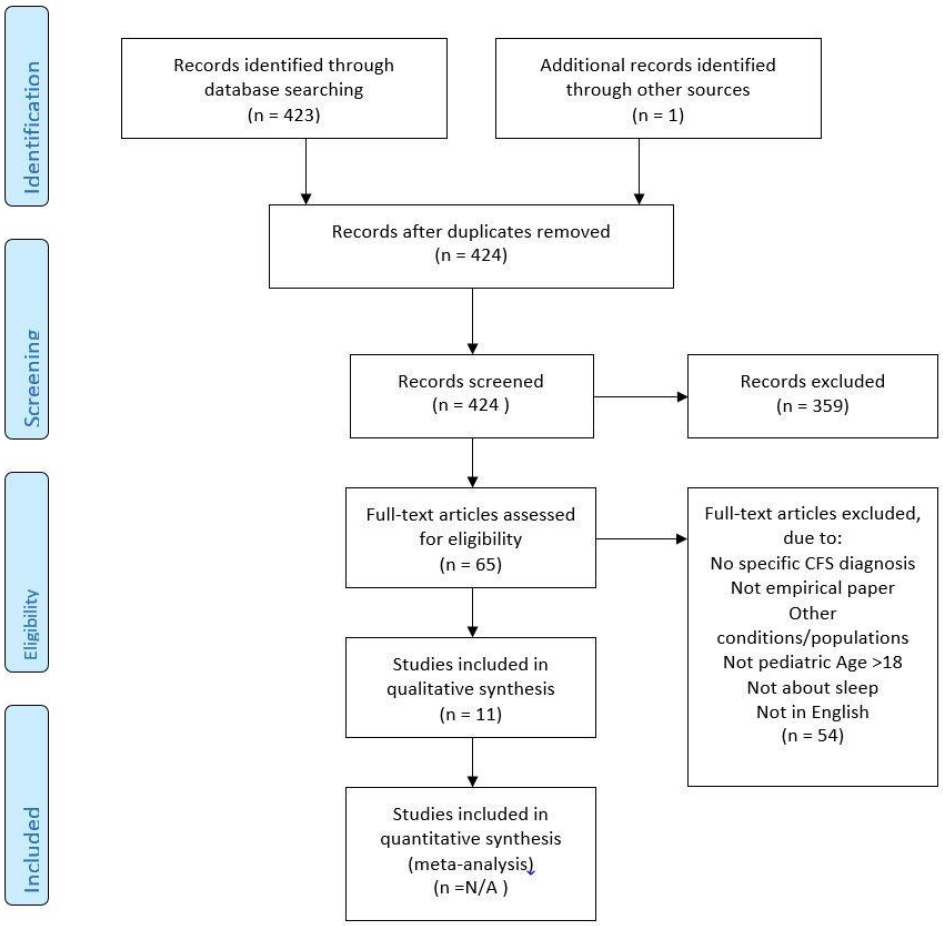
Information sources

The search was conducted through PubMed and reference lists were searched to identify any additional studies. The search was intentionally broad as we suspected there were few studies in this specific field of research and we wished to conduct a thorough search to maximize the number of studies found and subsequently included in this review.

Search

The following search was performed in January 2021:
((("chronic fatigue") OR ("chronic fatigue syndrome") OR ("myalgic encephalomyelitis") OR ("CFS") OR ("ME") OR ("CFS/ME") OR ("ME/CFS") OR (fatigue syndrome, chronic[MeSH Terms])) AND (("sleep") OR (Sleep[MeSH Terms]) OR Sleep Wake Disorders[Mesh] OR Sleepiness[Mesh] OR Sleep Medicine Specialty[Mesh] OR Sleep Aids, Pharmaceutical[Mesh] OR Polysomnography[Mesh] OR Sleep Phase Chronotherapy[Mesh] OR Circadian Rhythm[Mesh] OR “Circadian Rhythm” OR “actigraphy” OR "Actigraphy"[Mesh] OR “polysomnography” OR "Polysomnography"[Mesh] OR sleep* OR insomnia* OR dyssomnia* OR parasomnia* OR somnambulism OR somnolence OR hypersomnolence) AND ((“child*”) OR (“adolescent*”) OR (“infant*”) OR (“youth*”) OR ("Adolescent"[Mesh]) OR ("Child"[Mesh]) OR ("Child, Preschool"[Mesh]) OR ("Infant"[Mesh])).

We included in the search the terms “chronic fatigue”, “chronic fatigue syndrome”, “myalgic encephalomyelitis”, “CFS”, “ME”, “ME/CFS”, “CFS/ME”, “fatigue syndrome, chronic” AND “sleep”, “sleep wake disorder”, “circadian rhythm”, “actigraphy”, “polysomnography”, “sleep aids”, sleep phase chronotherapy”, “insomnia”, “dyssomnia”, “parasomnia”, “somnambulism”, “somnolence”, “hypersomnolence”, “sleepiness”, “sleep phase chronotherapy”, “sleep medicine speciality”, “sleep aids, pharmaceutical” AND “child”, “adolescent”, “infant”, “youth”, “child, preschool”. They were used as both specific key words and phrases and in MeSH-terms (Medical Subject Headings), as MeSH-terms are added after the article is reviewed and can be delayed significantly compared to the date the article is published. We specifically added more terms within the sleep research field to guarantee that the search would pick up even articles that did not use the word “Sleep” specifically.



PRISMA 2009 Flow chart

Study selection

Study selection was done based on the inclusion and exclusion criteria. The search turned up 423 articles, a great deal more than anticipated, but we opted to keep the search broad as many of the articles in the search were not relevant for this study and could easily be excluded. A number of studies outlined very vaguely the objectives and results in their abstracts and a significant proportion of the studies required full-text review to identify information such as age range of the subjects, whether sleep was a primary factor in the study and other exclusion and inclusion criteria. The articles were screened by one reviewer (JMES) and where there was any ambiguity around whether or not an article should be included or not, the supervisor (VBW) was applied to for guidance.

[103], one of the 6 articles included in the previous review on this topic, could not be found in full-text. The journal in which it was published has since been discontinued and the article is not found in PubMed or in the university library. It was decided to include the findings from this article based on the findings reported by Snodgrass et al. [29].

A meta-analysis was not possible due to the small amount of studies written on this subject. This was also the case for the last review by Snodgrass et al. [29] which only included 6 studies in total. The STROBE statement [104] was applied instead.

RESULTS

The ten studies included in this review are characterized by a wide variation with respect to the case definition, exclusion and inclusion criteria, sample size and the methods used to assess sleep. The demographic and clinical characteristics of the study samples are summarized in the four tables as outlined below:

Table 1) Study Design Characteristics
Table 2) Demographics of Study Population
Table 3) Characteristics of Participants Illness
Table 4) Clinical Characteristics of Study Sample

Study Design Characteristics

Seven of the ten studies were case-control and included control samples, and for these the recruitment was mostly done at specialized CSF centers or in hospitals. The recruitment of controls was either not reported, done through secondary school or college campaigns or in one case, Knook et al. [88] the patients were asked to suggest healthy friends. In two of the studies the participants were recruited either from ongoing studies on cohorts [18, 105].

The inclusion criteria, besides age, was either a prior diagnosis of CFS/ME, then later assessed by specialists, or a new diagnosis of CFS/ME set at a predefined hospital or CFS center. Additional screening was often performed, however the studies differ in their choice of exclusion and inclusion criteria.

In most cases having an ongoing psychiatric condition, other comorbid disorders or life situations, which may explain the fatigue, would be grounds for exclusion. This would sometimes be implicit through the chosen case definition used, but Collin et al. purposely included patients with comorbid depressive symptoms, arguing that 30% of children with CFS/ME in specialist services have comorbid depression [18] and it would be unreasonable to exclude them. Excluding them would also substantially reduce the number of potential participants and at some age points the prevalence of CFS/ME would even have been reduced by half.

The criteria for duration since the onset of symptoms differed from 2 to 6 months. Most case definitions for adults require a minimum of 6 months with severe symptoms before a CFS diagnosis can be confirmed, but the medical community is deliberating whether this is too long for this young group of patients [106].

Most studies did not report whether they required the participants to have a symptomatic sleep problem to participate, but [84, 103] required it, while Josev et al. [75] reported that they did not.

Some exclusion criteria seem to be of a practical nature, such as the ability to be fluent enough in English to complete the questionnaires or the difficulties in participating if the symptoms were so severe that the patient is permanently bedridden.

A common CFS case definition would have been beneficial, however no one definition was universally used, though the 1994 Fukuda criteria was prominent. This is also somewhat to be expected since there is an ever changing acknowledgement of what CFS/ME is, and the search for characteristics is ongoing. The British National Institute of Clinical Excellence (NICE) guideline from 2007 was used by Loades et al. and Collin et al. [1, 18], while Josev et al. [75] used the CFS/ME pediatric case definition produced by the International Association of Chronic Fatigue Syndrome Pediatric Case Definition Working group, and presented in Jason et al. [75]. In the last study a broad definition was applied, but all the participants were part of a larger pediatric study on CFS/ME, and it later was verified that 75% fulfilled the Fukuda criteria [105].

The methods used to apply the definition included clinical assessment at a specialist CFS unit [1, 75, 105], this could include pediatric assessment, blood samples, chest X-ray, brain MRI and abdominal ultrasound [105], while Collin et al. participants were not examined by physician upon entry [18] and the rest did not report on the methods.

Only two studies reported on the effort to ensure that the controls were healthy [1, 75]. Potential participants were recruited from schools/college, and were based on self-reporting. Eligible participants were selected against eligibility criteria; sleep disorders and psychiatric conditions. However for Josev et al., 11.6% of the recruited control participants had sleep conditions and 6.1% had psychiatric conditions [75]. The use of prescribed medications is another area which most studies did not report, but some explicitly stated use of medications as an exclusion criteria. For Pedersen et al. [105] this even included any use of hormonal contraceptives. Other drugs that were mentioned were antiepileptics or antidepressants [103].

Study Design Characteristics	Loades et al. (2020)	Collin et al. (2018)	Josev et al. (2017)	Pedersen et al. (2017)	Kawabata et al. (2013)	Ohinata et al. (2008)	Tomoda et al. (2001)	Knook et al. (2000)	Stores et al. (1998)	Ambrogetti et al. (1994)
Country	England	UK	Australia	Norway	Japan	Japan	Japan	Netherlands	UK	Australia
Type of study	Case-control	Population based study	Case-control	Cross-sectional	Case-control	Case-control	Case-control	Case-control	Case-control	Case series
Recruitment method	Recruited from 2 specialist CFS clinics	Participants from ALSPAC, birth cohort	Recruited from CFS/ME Clinic	Participants from NorCAPITAL, CFS/ME study cohort	Patients at hospital	NR	NR	NR	Recruited from pediatrician and ped. psychiatrist in area	NR
Recruitment timeframe	August 2010 October 2017	Birth cohort from April 1991 December 1992	December 2013 March 2015	NR	April 2007 Desember 2008	NR	1993- 1996	NR	NR	NR

CFS Case definition	Confirmed diagnosis NICE 2007	Research defined 'Chronic disabling fatigue CDF'	Jason et al. (2006)	75% adhere to Fukuda	Jason et al. (2006)	Fukuda 1994	CDC (Fukuda 1994)	CDC (Fukuda 1994)	Sharpe 1991	CDC 1988, (Holmes et al.)
Inclusion criteria	Diagnosis of CFS/ME	Diagnosis of CDF'; Lack of energy >6 months.	Diagnosis of CFS/ME; Primary complaint of sleep disturbance was not required	Fatigue for at least 3 months; Unable to follow normal school routines; Age ≥ 12 and ≤18 years.	Diagnosis of CFS/ME	Diagnosis of CFS/ME plus complaints of disturbed sleep	Diagnosed with CFS/ME plus suspected circadian rhythm disturbance	Diagnosis of CFS/ME with substantial decrease in activity;	Diagnosis of CFS/ME; Fatigue > 2 months; Seriously disrupted normal activities	NR
Exclusion criteria	Mental health problem (implicit by case definition)	Drug or alcohol problem; Eating disorder	English skills not sufficient. Unclear CFS/ME diagnosis. No medical or psychiatric condition to which the symptoms could be ascribed.	Being permanently bedridden; Disorders that may explain the fatigue (including demanding life events) ; Using prescribed pharmaceutical including hormone contraceptives	NR	NR	No physical or psychiatric disorder. Use of antidepressant or anti-epileptic drugs; Neurological illness; Migraine;	No medication at the time of the study or 6 weeks before; Patients with a psychiatric history	Other physical disease; Psychiatric disorder to which the symptoms could be ascribed.	NR
Methods used to apply definition	Assessment at specialist CFS units	Classified at age 13, 16, 18 based on questionnaires, no physician	Diagnosis at specialist clinic	Screening programme and study center	NR	NR	NR	NR	NR	NR
Medical investigations	NR	NR	NR	Reported	NR	NR	NR	NR	NR	Reported
Medical and psychiatric exclusions and co-morbidities - method of ascertainment	Clinical assessment	NR	NR	Clinical examination and assessment earlier screening	NR	NR	Psychiatric review	NR	NR	Psychiatric review, serological tests
Evaluation of controls	Reported	NR	Reported	NR	NR	Reported	NR	NR	Yes	NA
Ethical review reported	Yes	Yes	Yes	Yes	Yes	Yes	Informed consent	Yes	NR	NR

Table 1 Study Design Characteristics

Demographics of Study Population

The 10 relevant studies cover a time frame of 36 years, with the number of participants varying between 3 and 242. The study with the lowest number of participants was conducted in 1994, and

included no controls [107], while the largest number of participants can be found in a study from 2018, this one also having the largest number of controls [18]. The ratio between participants and controls was one to one in the early years [73, 88], then dropped to 50% controls or less [84, 103, 105, 108]. However in the most recent years the number of controls have increased with two studies having a ratio of 6 to 32 controls for every participant [18, 75]. Controls were either healthy (some studies checked for previous history of CFS or mental health problems) or they were included specifically for a health issue such as the asthma control group in Loades et al. [1].

The age of the participants were in the range from 9-21 years, but most commonly from the ages of 11-13 and up to 18. One British study divided the participants into races; 'white',' black', 'Asian' or 'others', and noted if they were ethnically British, unrelated to race [1]. Pedersen et al. recorded BMI (mean 21,5) and ensured the controls were in the same general area [105].

In the diagnosed adult CFS/ME population, the percentage of females is 60-65% [19]. The same ratio of female to male participants is noted in the most recent studies [1, 75, 105]. The studies in the Snodgrass et al. review from 2015 presented more variable ratios, from 41% females up to 80%. Overall, the studies are deficient in describing the characteristics of the participants, socioeconomic status is not reported, and even simple registrations as sex are occasionally omitted [18].

Demographics of Study Population	Loades et al. (2020)	Collin et al. (2018)	Josev et al. (2017)	Pedersen et al. (2017)	Kawabata et al. (2013)	Ohinata et al. (2008)	Tomoda et al. (2001)	Knook et al. (2000)	Stores et al. (1998)	Ambrogetti et al. (1994)
# of participants	121	242	21	120	70	12	41	13	18	3 (+1)
# of controls	101 - 23 w/asthma	7824	145	39	33	7	16	15	18	0
Recruitment rate %	89.6	NA	42	79.5	55	NR	NA	NR	NR	NR
Participation rate %	66.2	NA	NR	NR	84.3; controls 67.6	NR	NA	NR	NR	NR
Age, y	11-18	13-18	13-18	12-18	9-18	12-16	10-21	9-17	11-17	17 (45)
Race	Reported	NR	NR	NR	NR	NR	NR	NR	NR	NR
Ethnicity %	75 British	NR	NR	NR	NR	NR	NR	NR	NR	NR
Sex, % female	71	NR	62	72	50	75	41	80	44	66
Socioeconomic status	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
BMI	NR	NR	NR	Reported	NR	NR	NR	NR	NR	NR

Table 2 Demographics of Study Population

Characteristics of Participants Illness

The characteristics of the three studies in the Snodgrass review that included duration of illness, included participants that had been sick for years, from half a year up to 3 [88, 103] and up to 9 years [73]. Only two of the most recent four studies reported on duration and in different ways [75, 105], but the participants seem to have been sick for a shorter period of time, mostly from 1-2 years.

Only one study, Josev et al. [75] recorded which factors that were identified as a trigger or that exacerbated the illness. 'Infection' was the largest group with 58% (11), 32% (6) 'severe stress', 16% (3) 'immunization'. 11% (two persons) 'trip or vacation', 5% (one person) reported 'accidents', the last 16% (3) reported 'allergies, sinus' demanding sports, training schedule'. Unfortunately none of the studies included a symptom inventory.

In the study where medications were not an exclusion criteria the use of sleep aid is reported in 81% of the CFS patients in Josev et al. [75], while none of the controls reported use of any sleep aid. No serious psychiatric disorder or a psychiatric disorder that could explain fatigue were exclusion criteria for Stores et al., but 4 out of 18 participants were on antidepressant medication possibly because of effects on diffuse pain [73].

Characteristics of participants Illness	Loades et al. (2020)	Collin et al. (2018)	Josev et al. (2017)	Pedersen et al. (2017)	Kawabata et al. (2013)	Ohinata et al. (2008)	Tomoda et al. (2001)	Knook et al. (2000)	Stores et al. (1998)	Ambrogetti et al. (1994)
Duration of illness	NR	NR	<24 months 84%, >24 months 16%	Median 18 months	NR	NR	1-3 years	6–72 months; Median 13 months	5 months - 9.5 years	NR
Factors that exacerbate or trigger illness	NR	NR	Reported	NR	NR	NR	NR	NR	NR	Reported
Symptom Inventory	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
List of comorbid conditions in study population	NR	Depression	NR	NR	NR	NR	NR	NR	No serious psychiatric disorder, including depression or substance abuse	NA
Current prescribed medications	NR for CFS/ME, Asthma medications for asthma group.	NR	86% used sleep aid, 81% melatonin, 5% prescription sleep tablets; Control: no use of sleep aids	None - including hormone contra-ceptives	NR	NR	None last month	None last 6 weeks	4 on anti-depressant medication	NA

			or melatonin .							

Table 3 Characteristics of Participants Illness

Clinical Characteristics of Study Sample

Several different tools were utilized to capture sleep, anxiety, fatigue and depression, but the specific parameters and tools differ between the studies. Sleep questionnaires or sleep/wake diaries were often produced by the researchers themselves instead of validated alternatives.

Below is included a list of all the different tools in use.

For psychiatric review the following instruments were used:
Children's Depression Inventory (CDI) [109]
State-Trait Anxiety Inventory (STAI) [110]
4-item catastrophizing subscale of the Cognitive and Behavioural Responses Questionnaire [111];
Spence Children Anxiety scale (SCAS) [112]

For assessment of sleep quality the following instruments were used;
Karolinska Sleep Questionnaire (KSQ) or researcher-designed questionnaire
Researcher designed adolescent sleep/wake diary or questionnaire
Insomnia scale [113]
Pittsburgh Sleep Quality Index (PSQI) [114]
Other researcher designed sleep quality index
Accelerometer (activePAL single-unit uniaxial accelerometer)
Actigraph
Polysomnography (PSG)
Core Body Temperature measurement
Multiple Sleep Latency Test (MSLT)

For capturing the level of fatigue or functioning the following instruments were used:
Chalder Fatigue Questionnaire (CFQ)[115]
Short Form 36 Physical Functioning Scale (SF-36PFS) [116]

Studies on minors may rely on observations done by both parents and the child. In the Collins et al. study [18], the questionnaires used to classify the children from the population study as having CDF/ME-like symptoms, were completed by parents at age 13, by parent and child at age 16 and by the child only at age 18.

These tables emphasize the difference between the studies and the difficulty in comparing them. There are several case definitions in use, and no symptom inventory. The sample sizes and characteristics of the samples vary, and as did the methods used to assess sleep, the parameters

measured, duration of data collection and the investigation of other biological factors that could alter sleep.

Clinical characteristics of studies	Loades et al. (2020)	Collin et al. (2018)	Josev et al. (2017)	Pedersen et al. (2017)	Kawabata et al. (2013)	Ohinata et al. (2008)	Tomoda et al. (2001)	Knook et al. (2000)	Stores et al. (1998)	Ambrogetti et al. (1994)
Tools	CDI; Insomnia Scale; physical functioning SF-36PFS; CFQ; STAI;	ALSPAC questionnaires from database	Actigraph, Sleep-Wake diary, self-rated PSQI, SCAS, parent questionnaire	Uniaxial accelerometer, KSQ	Actigraph	Actigraph; sleep/wake diary; questionnaire	NA	Cotton for saliva melatonin level; research designed sleep questionnaire	PSG	PSG; MSLT
Primary and secondary outcomes	Measure of sleep, Fatigue, physical functioning, anxiety, depression and catastrophizing	Sleep duration	Sleep quality, relationship between objective and subjective measures, association sleep/ anxiety	Sleep/wake rhythm; perceived sleep	Time in/out of bed; rest and activity bouts	Total sleep time, frequency of extremely long sleep; activity	Amplitude of CBT variation, appearance time of lowest CBT, circadian variation in cortisol	Nocturnal rise in melatonin; sleep quality	Total sleep time, sleep latency, # of awakenings, NREM sleep stages, REM sleep latency and %	NR
Measures, environment and duration	1-2 scheduled appointment for questionnaire completion, 3 months apart	Sleep questionnaire from database 0-11 years. 'CFS/ME', questionnaire at 13, 16, 18 years	Actigraphy home, 2 week (measured only school nights); questionnaire	Accelerometer 1 day hospital, rest of week home	Actigraphy, home, more than 3 days	Actigraphy, sleep/wake diary, home 2 weeks	Daily sleep/wake diary, CBT, circadian rhythm of cortisol (4 weeks or longer)	Weeknight home for salvia sampling;	PSG, home 1 night	Polysomnography, laboratory 1 night
Self-reported functional impairment, levels of activity	Yes	Yes	Yes	NR	NR	NR	Yes, Performance status score	Yes	NR	NR
School attendance	NR	Absence from full time school OR prevented from other activity 'quite a lot'	Parent questionnaire	NR	NR	NR	NA	NR	Majority missing long periods of schooling	NR
Language used to collect data	English	English	English	Norwegian	NR	NR	NR	NR	NR	NR
Missing data management	Imputation, assuming missing values were missing at random	NR	NR	NR	Participants excluded if data insufficient or clearly abnormal	NR	NR	NR	NR	NR
Statistical methods reported	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	N/A

Table 4 Clinical Characteristics of Study Sample

Study findings

Out of the 10 studies included in this review 8 of them had a control group with healthy controls, and one included an illness control group (asthma patients on medication). All of these studies found that sleep was disturbed in one way or another compared to the controls though the findings did not always agree. 5 of the studies found subjective, objective or indirect evidence of longer SOL using questionnaires and actigraphy. This is in contrast to the 2 studies which utilized PSG which found no differences in SOL between CFS patients and controls. 3 studies found longer TST, though one of them only significantly different from controls on weekdays [105]. The same 2 PSG studies found similar results for TST in both groups. Most of the studies with the exception of Josev et al. [75] found more awakenings in the CFS group, though reporting on SE was more erratic. Some studies suggested similar bedtimes, but found later rise times, though they speculated that this specific CFS group might not be required to attend school in the mornings because of lower school attendance rates. The studies which found longer TST used actigraphy which is known to overestimate TST, and SE, so the participants may have been lying in bed, just very still.

Josev et al. found that objectively using actigraphy participants with CFS had significantly longer SOL, TIB, TST, and later RT, although similar levels of SE, BT, and WASO as the control group [75]. They also recorded subjective data which found that CFS subjects self-reported poorer sleep. Surprisingly, the subjective sleep scores in this study did not correlate to any of the objective sleep measurements for the CFS participants. Illness duration, school attendance and electronic device use were all found to not predict any measurements of sleep quality, neither subjective nor objective.

Another finding in this study was that the CFS group showed significantly higher levels of anxiety than the healthy controls**.** However the level of anxiety was not found to correlate with any objective measures of sleep quality, although a higher level of anxiety was significantly associated with greater subjective severity of sleep disturbance, as reported on the PSQI. This indicates that perception of quality of sleep is influenced by psychological factors, even when they do not significantly contribute to disruption of sleep.

Pedersen et al. found that CFS participants spent an equal amount of time in bed the entire week in contrast to the regular pattern of weekend jet-lag in the control group [105]. They spent longer time in bed than their peers and exhibited a later mid-sleep time during weekdays. Using subjective scoring they scored significantly lower on all items on the KSQ with the exception of snoring. Especially low were the scores on sleepiness, insomnia and awakening problems. Furthermore the CFS participants reported longer sleep onset latency than the control group. 10% of the CFS group showed signs of delayed sleep-wake phase when compared to the rest of the participants.

Ohinata et al. [84] managed to divide the CFS subjects into subgroups based on their sleep pattern, into an irregular sleep type (IR group) or a delayed sleep phase sleep type (DSP group). The IR group had an impaired circadian rhythm with daytime naps and disrupted nocturnal sleep. The disruption of sleep in the IR group was demonstrated by a higher VSS index, indicating a higher percentage of sleep less than 180 min of total sleep time and a very low DTA index, compared to the controls and the DSP group, indicated a disrupted circadian rhythm. The DSP group kept their circadian rhythm without sleep disruption.

They found that the CFS group experienced extremely long sleep, defined as >10 hrs of continuous sleep. The highest frequency of extremely long sleep was in the DSP Group characterized by mostly

uninterrupted sleep. It was not observed in the control group. The CFS group also showed decreased physical activity compared to the control group and significantly longer TST.

Stores et al. found differences in sleep physiology between CFS patients and healthy controls [73]. With PSG they found that CFS participants suffered from more disrupted sleep in the form of more awakenings of various lengths. This greatly reduced sleep efficiency in this group. The authors noted that some of these awakenings were so brief that they could easily be missed by using other sleep measure methods such as actigraphy. They observed less NREM stage 2 sleep in CFS patients and less percentage of REM of total sleep, but the latter effect disappeared when they excluded the 4 CFS participants using a tricyclic antidepressant or SSRI, suggesting this effect might be medication induced. The slow wave sleep (SWS), defined as NREM sleep stages 3 and 4, was not different between the two groups. TST and SOL were not significantly different in the two groups.

The two most recent studies looked at sleep over time; Loades et al. found sleep problems tended to decrease over time and that sleep at baseline predicted some of the variance in sleep at 3 months, even when biases were taken into consideration [1]. Still, depression, trait anxiety and catastrophizing accounted for about ⅔ of the variance in sleep. Interestingly, sleep at baseline did not predict fatigue or function at 3 months. Collins et al.[18], the only study using a longitudinal design, found that shorter night sleep between 6 months and 11 years significantly raised the odds of having a CFS-like condition as at 13, 16 and 18 years. The study did not define the patients as CFS patients since the information was based on parent and child reported questionnaires about fatigue, sleep and activity. They also found a tendency to have more awakenings at 6 months, 6, 7 and 9 years. Trouble initiating sleep was common in the CDF group. This longitudinal study found that the majority of the participants who fell into the CDF category, only had this at one point of the study, meaning most of the cases improved or resolved completely between 13 years and 16 years, 16 years and 18 years.

Kawabata et al. found the distribution of DOWN and UP periods as a marker for activity and rest was different over time using actigraphy. The temporal distributions from the collected data showed no differences during activity, but the rest periods had a lower tendency to favor the exponential distribution among CFS patients. The authors speculated if the results could be due to disturbed sleep patterns in children with CFS [108].

Knook et al. found that the CFS group reported having more restless sleep, waking up feeling unrefreshed and reported more awakenings at night [88].

Ambrogetti and Olson [107] showcased 4 cases where the CFS diagnosis had been made and then later reclassified as narcolepsy as a cause of at least a good portion of the symptoms. All cases exhibited excessive daytime sleepiness as the main symptom in contrast to fatigue, which is often defined more as tiredness rather than sleepy. They all underwent PSG testing and was diagnosed with the sleep disorder and subsequently medicated. This article was published before the era of CFS/ME as a diagnosis of exclusion and argued the importance of primary sleep disorders as a possible differential diagnosis, as well as added to the discussion of whether sleep disorders can occur concomitantly with CFS or if they are mutually exclusive. That debate is still ongoing.

Biological markers related to sleep were recorded in two studies. Knook et al. investigated melatonin patterns and levels in CFS patients and found surprisingly higher levels of melatonin in this group [88]. They did not find the delayed pattern effect which they were expecting. Tomoda et al. [103] used core body temperature, to examine if CBT is altered in CFS patients who experience disturbed sleep. They found a decreased amplitude variation in the CBT recorded in CFS patients as well as that the lowest recorded CBT came later.

DISCUSSION

CFS is a debilitating disease that can have huge consequences especially when it debuts in the vulnerable period of childhood or adolescents. Sleep disturbances in this population are common [3, 4], but little research has been conducted on this topic. This study aimed to summarize existing literature on sleep disturbances occurring in CFS/ME in the pediatric population. Snodgrass et al. systematically reviewed the literature in 2015 and discovered only 6 articles with over all small sample sizes, varying definitions and other methodological problems [29]. 6 years and 4 articles later the field is still jumbled and no clear pathophysiology has surfaced through the new research.

A total of 10 articles, 4 in addition to the ones identified by Snodgrass et al. [29], were included in this review after a very broad search of literature. The studies all reported more sleep disturbances in pediatric CFS/ME patients. This coincides with the results presented by the last review in 2015 [29] and solidifies sleep as an important aspect of CFS/ME both in diagnostics and future treatment. The majority of the studies included both subjective and objective measures, painting an increasingly detailed picture on what types of sleep disturbances and the effects it has on patients. However the relationship between subjective experience of sleep disturbances and objective assessment is likely more complex. Although the subjective data reported more trouble initiating sleep, more restless sleep, more awakenings and non-restorative sleep, the objective data was less consistent, and at times contradicting the subjective reported data. This is in line with research done in adult CFS where much of the research on the topic has been inconsistent between studies and has varied much [20].

Stores et al. is still the one study that has looked at sleep architecture in the pediatric CFS/ME population [73]. It reported reduction of NREM stage 2 sleep and REM sleep. Snodgrass et al. recommended more research to aid in the understanding of sleep stage dynamics in pediatric CFS/ME, but no new studies in the pediatric population have been conducted [29]. Several studies on adult CFS however, have found inconsistent findings [20]. Reduction in SWS is one of the proposed culprits of non-restorative sleep, but the recordings have not been consistent. More research into the microstructure of sleep in CFS/ME may hold some of the answers.

Two of the studies in this review included biological markers and both presented surprising results. Knook and colleagues found higher levels of melatonin in the CFS group, suggesting melatonin based sleep aid should not be recommended in this population [88]. However as pointed out earlier, findings regarding melatonin have not been consistent. Tomoda et al. looked at CBT, another biomarker that has failed to produce reliable results [103].

In the earlier studies many hoped to find a biomarker that could be used to distinguish CFS from other comorbidities, and several adult studies focused on this. This was proven difficult, and has resulted in conflicting results and no clear marker for CFS has emerged as of yet. Some markers have only been evaluated in one single study, either due to expenses or being impractical. It is not clear if we will have a biological marker in the future, neither in a research nor clinical setting.

Difficulties in comparing studies

Although the trend is towards larger studies and more comprehensive reporting on items such as participant demographics, study protocol and methodology, the articles included in this review overall vary widely. The use of various case definitions, including and excluding based on different criteria, different methods to assess possible differential diagnoses and the heterogeneous nature of the study population, makes statistical analysis and comparisons of the findings difficult to conduct.

If the trend continues however we may hope to unlock possibilities for cross-study statistics which could reveal specific information that might give insight to underlying pathophysiology and create new avenues of research. Still, several other obstacles make comparison difficult.

A challenge which arises when trying to compare these studies is that participation and recruitment varies quite a bit and selection bias may occur. CFS/ME is a taxing disease where patients have little energy to spend each day and experience post-exertional malaise. The studies that reported on recruitment and participation, acknowledged the tendency to recruit more high functioning patients, which is not uncommon in CFS/ME research due to the impact on everyday life. Josev et al. discussed this as the participation rate was only 42% in their study [75]. This makes it harder to generalize the findings to the entire CFS population.

Some of the patients attending the clinics and hospitals, where the participants are usually recruited, are so ill they are mostly bedridden and wear dark sunglasses and noise cancelling earplugs, as they arrive in a wheelchair to attend an appointment. To have the energy to read the questionnaires and concentrate for long enough to fill them out, to get to a sleep recording center and stay the night with lots of new people and stimuli, is not something every CFS patient can manage. Even those who participate may experience a rebound effect. Some patients may want to prioritize what little energy they have on some of the things they frequently miss out on like spending time with friends or attending school. Some concerned parents, perhaps with little experience and knowledge about the condition, may be too overwhelmed or overprotective to allow for participation, fearing the extra tasks may trigger an exacerbation. This being the nature of the disease may thus cause bias as recruitment rates are low and generally does not include severe or even moderate CFS/ME. Loades et al. recognized that since all their recruitment was done through specialist clinics, the findings might not be applicable to the general CFS/ME population, but rather those patients found in such clinics [1].

How highly functioning the participating patients are may affect study results as well. School attendance has been used as a marker for function in children and adolescents and when reported, varies significantly. Josev et al. discussed the possibility that their results, which showed that CFS/ME spent more time in bed, woke up later and experienced more difficulties in initiating sleep, may be influenced by that the part of the CFS/ME group that did not attend school and thus was not required to wake up early as their healthy peers and could stay in bed for longer [75]. The authors suggested that the CFS patients possibly were trying to compensate for their poor sleep, to avoid feeling unrested [75]. They also acknowledged that the result may reflect the heterogeneity of this group. Thus the research findings are hard to extrapolate to the larger CFS population.

Participation after the initial inclusion in a study could also be hampered by several factors. Loades et al. noted that only about ⅔ of the participants returned for the second appointment which was scheduled for treatment initiation. They reported that the reasons for dropping out was due to economic problems or that the patients did not require or want treatment [1]. This could mean that the study skewed results in unforeseen directions by possibly omitting patients from families with lower socioeconomic status, patients that had their fatigue issues quickly resolved, patients that had become worse regretting saying yes to attending due to very low energy levels, and patients skeptical of official treatment guidelines (much fear mongering in social media and forums may have put some families off from receiving treatment).

The heterogeneity of the participants have also been criticized. One aspect of this is what sort of treatment the participants have received before initiating the study. Not all studies reported on this, but as an example, Loades et al. reports that standard treatment given to every patient upon

diagnosis in Australia is sleep hygiene advice and according to their sleep pattern and problems they may receive a prescription for a sleep aid such as melatonin [1]. Sleep aids have been shown to impact results in PSG and failure to declare medication could skew the conclusions later. Stores et al. [73] even deliberately reevaluated the results, excluding the CFS patients on medications from the dataset, and the differences he had found in the proportion of REM sleep were no longer significant. However the difference in sleep physiology between the CFS patients and the control group was still there, implying some, but not all of the results were medication induced.

Although the studies which reported on subjective measures of sleep quality commonly did this using a sleep assessment questionnaire, not one of them ended up using the same questionnaire. Five of the studies even used a researcher made questionnaire rather than a standardized, validated one, making the results harder to trust[15, 18, 75, 84, 88]. This is another factor that complicates comparing the reported data.

This inconsistency in methodology could be said to be symptomatic of the whole research field of sleep in pediatric cases. The issue is again the lack of consensus on sleep assessment in the pediatric CFS/ME population. There are not many sleep questionnaires which are validated for children and adolescents. PSQI, which was used only by Josev et al., is one of the most widely cited sleep questionnaires used in research [75]. Although it was not made for the pediatric population, it has been validated for adolescents [114]. This could make it a good candidate for future studies. The variability in sleep questionnaires could also reflect that each questionnaire is a little better at highlighting one or several aspects of sleep and in some cases they probably chose a questionnaire tailored to their study and what they wanted to find.

We also found that the sleep research field uses different nomenclature. Ohinata et al. showed the percentage of sleep less than 180 minutes of the total sleep time by the use of VSS index, while other studies used WASO for measurement time awake after sleep onset [84].

Discrepancies of findings

The frequent inconsistency even in objective findings illustrate the challenges tied to research on sleep in CFS/ME and may be due to several factors. Below are some factors that may explain in part why the results differ.

Heterogeneous studies of varying quality

Heterogeneity in case definitions, the use of different sleep assessment tools, inadequate size of study samples, differences in study setting (home/clinic) and an inherent heterogeneity of this population may all explain why results may vary across studies. The participants in the studies varied markedly on all the following factors; duration of the disease, age at onset of illness, whether and what treatments had been received, as well as the degree of comorbidities. However several studies which have been of higher quality, conducted in adults, also report differential objective findings. Selection bias, as previously discussed may apply to both adolescent and adult CFS/ME and also be part of the reason for the divergent findings.

Definition encompass more than CFS/ME

Some have argued that that the operational definition of *CFS/ME* is too wide and could result in the inclusion of other illnesses such as depression or psychosomatic illnesses. They argue that a more precise definition is needed, which restrict research to actual CFS/ME cases, in order to discover how

sleep quality is affected by the disease. This has proven difficult as comorbidities are common and no markers or specific characteristics of the disease have been identified yet. Twin studies with identical twins discordant for CFS/ME could be a design which would reduce confounding due to a wide group of genetic and environmental factors, but these studies are few and hard to come by.

Counter arguments around comorbidities

Others have argued that recent research indicates that several of the diagnoses excluded today should very well be seen as comorbidities. This includes psychiatric disorders such as anxiety, depression and primary sleep disorder [20]. Researchers have found that fatigue and CFS/ME symptoms are not completely diminished by treating these diagnoses and suggest that CFS/ME is a separate diagnosis.

Arguments for a wide definition

Others yet argue that the inconsistency in research results indicate that CFS/ME might be a continuum and that wide definitions are necessary. Several studies have found no differences between CFS/ME patients that fulfill strict criteria compared to patients defined by a wider criteria [105, 117-120], or they find a significant overlap [121]. They argue that the lack of biological markers, lack of objective findings and a wide range of possible triggers of disease, in distinguishing cases defined by either strict or wide criteria suggest that CFS/ME are not inherently different across these groups. This suggests a more functional disorder and may require a more holistic, multifactorial approach.

Objective assessment not sensitive enough

Preliminary research results suggest that traditional sleep assessment methods may be inadequate to pick up differences in microstructure of sleep in CFS/ME. Several more sensitive methods have been explored with varying results [20]. This has yet to be explored in children and adolescents. Better quality of future studies in this field should help clarify some of these uncertainties.

Different objective assessment tools

Subjective SOL is found to be significantly longer in all studies which have included this measure. It is interesting to note that SOL was increased in the CFS/ME group in the two studies that utilized actigraphy while no significant difference were reported in SOL in the studies which employed PSG. As discussed previously, there are limiting factors tied to the use of each method. This may explain some of the discrepancy in objective findings.

Sleep misperception

Some have proposed that CFS/ME patients may suffer from sleep misperception as an explanation for the discrepancies. The argument is that CFS/ME patients may overestimate their poor perceived sleep and thus create the mismatch between subjective and objective findings. Overestimation of poor sleep and underestimation of SE has commonly been reported in patients with inferiorly perceived health and symptoms of depression [20, 122]. Still, sleep disturbances are common in CFS/ME patients both with a psychiatric comorbidity and those without it [20, 61, 62]. Jackson et al. suggest in their review that overestimation of poor sleep is more likely a global phenomenon among patients suffering from poor sleep than a strictly CFS/ME problem [20]. Harvey suggests that patients with insomnia are highly tuned in on how well they sleep and awareness of their daytime function [123]. The overly negative focus on sleep causes both autonomic arousal and emotional distress which may cause the patient to become hyper aware of sleep threats. The sad outcome of triggering this alarm system is that accumulation of anxiety surrounding sleep can lead to very real consequences for actual sleep and functioning [123].

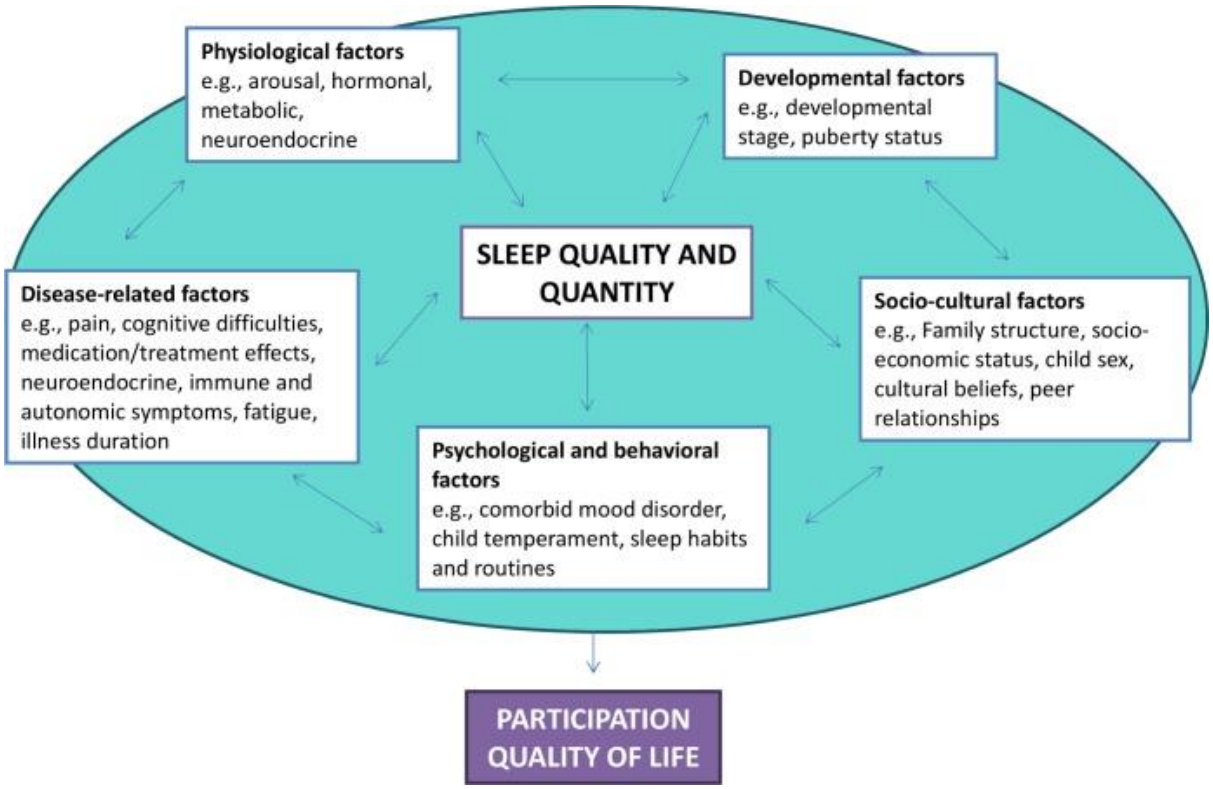
Sleep phenotypes

Another possibility is that the inconsistencies are due to a lack of a unitary sleep profile in CFS/ME, as there may exist several. This was first proposed by Ohinata et al. [84] who found that they could subdivide their CFS/ME group into cases with two different types of sleep patterns. This has also been discussed later by Josev et al. [75].

Central unanswered questions

As discussed in this review CFS/ME patients experience more sleep disturbances than controls and it has a significant impact on their life and mental wellbeing. But what causes the sleep disturbances experienced by CFS/ME patients?

We have very little evidence regarding the causes of sleep disturbances in CFS/ME. As we have discussed in this article several factors impact sleep and the final answer might be multifactorial. Snodgrass et al. [29] suggested a model that ties together all the different factors that influence sleep quality and quantity. It illustrates how complex sleep can be, but also has the positive highlight that there may be different paths that may be explored in the search for treatment.



Some of the questions we ask when trying to find causal factors of sleep disturbances in CFS/ME are firstly if these sleep disturbances are inherently something to do with the underlying pathophysiology of the disease (in Fig 1)? Or are they inherently caused by the symptoms CFS/ME patients experience (in Fig 1)? Or are they inherently caused by general mechanisms that occur when a patient is chronically ill? Loades et al. tried to compare CFS/ME patients to an illness control group to find evidence for the latter, but conceded that asthma patients were probably an inadequate comparison [1]. It is a true challenge to discern whether the sleep disturbances has a causational role in the disease, are a consequence of the underlying mechanisms and pathophysiology, or are a consequence of other symptoms related to CFS.

Other questions yet unanswered is whether we find more anxiety and depression in CFS/ME patients because a common unknown factor, such as an environmental or genetic factor, predisposes for these diseases (an unknown , perhaps)? Or is it because CFS/ME causes sleep problems which are known to predispose for mood disorders? Or may factors tied to the disease

(invisible, low status, no cure, unknown prognosis, patients fear that something is seriously wrong with them etc) cause anxiety and depression? The debate is ongoing and the research community is split on this issue.

Although we in research separate sleepiness from fatigue, this has proven to be more complicated in clinical practice. It is still uncertain whether CFS/ME causes both fatigue and sleepiness as a primary symptom or if sleepiness is a symptom secondary to other disturbances caused by CFS/ME such as anxiety and depression.

Sleepiness could also be a symptom secondary to bad sleeping habits (sleep hygiene) or lack of routine/schedule commonly seen in CFS/ME patients. Or is sleepiness could be tied to the co-occurrence of a primary sleep disorder?

In conclusion a good tool to differentiate the different types is needed as discussed in Jackson et al. two [20]. A good assessment tool is crucial to clarify the origin of sleep problems further.

One exercise I did when I worked on this complex topic was to begin with one factor and make a continuous line of factors relating to poor sleep from there. One pathway would be *CFS/ME -> fatigue -> reduced demands/function -> reduced routine/schedules -> reduced sleep pressure/slacking of sleep hygiene -> sleep disturbances -> sleepiness/fatigue/less structure/compensate poor sleep by sleeping longer into the day.* Numerous alternative "causal chains" can be drawn when discussing sleep in CFS/ME in children and adolescents. The whole picture is so complex and characterized by bidirectional interactions between most factors. Future research needs to be structured around specific chains of mechanisms to bring this field forward.

Future research

In conclusion the field is characterized by a low number of total studies of varying quality and with inconsistent results. More research is crucial to understand the complex relationship between sleep and CFS/ME in children and adolescents. As discussed future studies needs to be of sufficient sample size, with well-defined study populations, and include a complete characterization of all symptoms and comorbidities. Comparisons needs to take into account the duration of illness and received treatment amongst others. It would be useful to note triggers of disease and triggering factors for exacerbations, and whether such factors determine subgroups of CSF/ME. Research on treatment should optimally focus on participants not on any medications or if not possible adjust for medications in the analysis, as this could influence results [73]. Since many pediatric CFS/ME patients have disease onset in the early teens, concurrently with normal sleep maturation, pubertal status could be an important factor to take into account. Age is not an optimal surrogate for pubertal status. Instead instruments such as Tanner staging or hormone testing should be used which would be an accurate method of defining maturation.

Attention also needs to be given to controls, which optimally should be drawn from the reference population and well matched. The registration of medications [73] and properly screening for sleep disorders and psychiatric comorbidities in controls, is important, especially in adolescents.

Also another patient population can be used as a control group for certain research questions. They need to be selected thoughtfully. Asthma patients, for instance, is a bad choice as quality of life and disrupted function and school attendance is not comparable to the levels seen in CFS/ME patients [1].

Future studies should include cognitive, behavioral, objective and subjective sleep measures in order to get an extensive understanding of sleep disturbances in the pediatric subgroup of CFS [20]. Factors that are important for sleep, such as sleep hygiene should also be mapped. The Adolescent Sleep Hygiene Scale [124] can be used to map amount of screen time before bed and other sleep hygiene factors in adolescents. BMI, physical activity and other factors should also be included [1].

As Snodgrass et al. pointed out [29], little is known about the natural course of sleep disturbances in CFS/ME over time and longitudinal studies are needed to look at progression, impact and prognosis. This could also help identify factors that have a role in triggering and perpetuation of CFS in pediatric CFS/ME [73]. It could provide predictors for later function, fatigue or sleep quality. Impact of sleep also needs to be better understood, e.g. consequences for participation, daily function and quality of life. Loades et al. suggests using the School and Social Adjustment Scale to better observe impacts on school attendance [1].

Objective assessment of sleep should include more sensitive methods of EEG recording to clarify if differences in microstructure of sleep [20]. The methods could be improved by not enforcing wake and bedtimes, to simulate more natural settings. Most of the studies with objective measures have focused on nocturnal sleep. Including daytime naps could be important as many patients sleep a lot during daytime as well. Since adolescents display 'social jetlag', indicating weekdays vs weekends could also be useful. Twin studies could be of great help in discovering new CFS/ME specific factors, since this design eliminates a wide array of environmental and genetic factors [20].

More research on how sleep impacts fatigue and vice versa is much needed. However, as argued by Jackson et al. in their review we first need better methods to differentiate 'sleepiness' and 'fatigue' [20]. This is not an easy task but an improvement would be to develop a questionnaire that maps both symptoms.

A study of CFS/ME patients during performing difficult tasks found altered neural activity. Neuroimaging while observing functions and blood flow during sleep could represent a possible new avenue of research after [20].

Further research is needed to confirm the effect of sleep interventions in children and adolescents with CFS/ME. Sleep disturbances are found in pediatric CFS/ME patients and they represent possible avenues for treatment to alleviate symptoms, improve function and quality of life in this population. The results of this study has shown that perception of sleep and emotional distress could impact perceived sleep problems negatively. Working to change erroneous beliefs about sleep and treating concurrent anxiety and depression could have a positive impact. Furthermore, as longer SOL is observed in this patient group, indicating difficulties falling asleep, validated treatments for insomnia such as cognitive behavioral therapy should be trialed [125]. Lastly, as many of these patients lose structure in their daily life, sleep excessively to avoid feeling unrested and exhibit sedentary activity patterns due to pain and fatigue, special care should be given to restore a normal structure and general sleep hygiene techniques [126]. Some preliminary data suggest that treating sleep problems could work well in children and adolescents with CFS/ME, alleviating symptoms and increasing function[84, 127]. More research is needed to find what treatment would help the most.

Limitations of this study

This review used the PRISMA method from 2009. A new PRISMA statement was published in 2020, which could be superior to the 2009. However it was decided to use the 2009 version to ease comparison with the review by Snodgrass et al. Although this is a recognized and validated method for producing systematic reviews it is not without faults. We could have missed some studies when screening the currently published research and a limitation of this review is that only the PubMed database was searched. Although most literature is published in English, a decent amount of the research has been produced in Japan and there is a risk that excluding non-English articles could have caused us to miss some relevant studies. The limitations of the studies included in this review makes it hard to generalize any of the findings of this review.

CONCLUSION

CFS/ME is a complicated disease and has a huge impact on the daily lives of patients. Sleep is a big part of the symptoms, but little research has been done on children and adolescents with CFS/ME. 4 more studies were identified since the previous review by Snodgrass et al. [29]. The results of this study point towards greater subjective sleep disturbances in this population such as longer SOL, more awakenings and non-restorative sleep. Objective measures have been more inconsistent. Anxiety and depression seems to have an impact on perceived sleep and other symptoms and such be targeted with treatment. Many unanswered questions about the characteristics and causes of sleep disturbances in pediatric CFS/ME remains and more research is needed.

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