Sleep and Activity Patterns of Children with Down Syndrome
in Relation to Sleep Disordered Breathing

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Abstract

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Background and purpose: Sleep disordered breathing (SDB) is a major health problem in children with Down syndrome (DS), and may adversely affect not only health, but also accomplishment of life's daily activities and habits. Obesity is a known risk factor of SDB in the general population, but in children with DS there have been conflicting reports on the role of obesity in SDB. The goal of this dissertation is to: 1) review the current state of knowledge in sleep of children with DS; 2) describe sleep patterns, and examine the relationship of sleep disturbances, including SDB, with the accomplishment of daily life habits; and 3) describe activity patterns, and evaluate the relationships between SDB, sleep duration, obesity and physical activity (PA) in a sample of children with DS.

Methods: A review of the English language literature between 1960 and 2012 was completed, studies were described and synthesized. An Internet sample of 139 parents of children ages 5 to

18 years (110 parents of children with DS, 29 parents of children with typical development [TD]), completed a 45-minute online survey. The survey included previously tested and established subjective instruments on sleep characteristics; the Children's Sleep Habits Questionnaire (CSHQ), the Life Habits Questionnaire (LIFE-H), and Children's Physical Activity Questionnaire (CPAQ). Patterns of sleep, life habits accomplishment, and PA were described and compared between children with DS and TD. The associations of sleep indicators with life habits accomplishment, and SDB and sleep duration with obesity and PA were evaluated in a series of regression analyses.

Results: The presence of SDB in a large proportion of children with DS is well documented in the literature. Sleep disturbances did impact the accomplishment of daily life habits over and above the impact of DS itself. The impact of SDB on life habits accomplishment figures prominently among eight measured domains of sleep disturbances. While children with DS had longer sleep duration compare with children with TD, SDB is a significant explanatory factor in duration of sleep among all children. Presence of SDB symptoms was associated with a 38-minute decrease in sleep duration (95% confidence interval [CI]: 12- 64 minute decrease, probability [p] =0.005). A dose response relationship was observed between overweight and SDB. Obese children (body mass index $\geq 95^{th}$ percentile) had almost a six-fold risk for presence of SDB symptoms (odds ratio [OR] =5.78, 95% CI=1.90-17.61, p=0.002). Every hour increase of moderate to vigorous PA was associated with a 13% reduction in risk of obesity (OR=0.87, 95% CI=0.78-0.96, p=0.006).

Conclusions: SDB is a major contributor to compromised accomplishment of daily life habits in children with DS. Overweight and obesity are implicated in contributing to SDB.

Interventions for increasing PA and reducing obesity in children with DS have the potential to decrease the symptoms of SDB and improve the accomplishment of life habits and life quality.

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Dedication

To Dean, Berkeley, and Brandon Churchill

Introduction

According to national data from ten regions of the United States, the survival of children born with Down syndrome (DS) has improved significantly since the 1980s (1), signaling continued increase in life expectancy. Moreover, the Centers for Disease Control and Prevention (CDC) reports a 24% increase from 1979 to 2003 in the number of births affected by DS; and an increase in the rate of live births of DS, from 9.5 per 10,000 live births in 1979 to 11.8 per 10,000 live births in 2003, in the same ten regions of the United States (2, 3). This increase in births, survival, and life expectancy of individuals with DS has major implications for the management of health care and wellbeing of this population. Congenital heart defects are present in about 50% of infants with DS (4). While life-saving surgical procedures for correction of congenital heart defects early in life have contributed to increased survival and life expectancy, individuals with DS are at increased risk for other health problems, including sleep disordered breathing (SDB), which first came to attention in the 1980s (5). Improved quality of life and health must accompany improved survival and life expectancy. Clinical management of SDB, as well as family- and healthcare-initiated primary and secondary preventive measures, are essential for improving health and life quality in DS.

With a framework of prevention, and using a theoretical model of the role of night-time sleep—and fragmentation or loss thereof—in performance of daytime activities (6), the goal of this dissertation was to bring to light the interworkings of mechanisms that may contribute to the successful accomplishment of daily life activities in children with DS that relate to sleep. To begin, a comprehensive review of the literature, between 1960 and 2012, was completed to synthesize current knowledge and the state of science in measuring and monitoring sleep in children with DS. The review includes an epidemiologic overview of DS and the historical context of developing technologies for measuring sleep. The review forms the first chapter of this dissertation.

The second and third chapters report the results of an Internet survey of parents of children with DS who responded to questions about sleep and daily activities of their children. The second chapter examines the relationship of sleep disturbances, including SDB, with accomplishment of daily life habits of children. The third chapter is an examination of the relationship of SDB with obesity and physical activity. Each of the first three chapters form related but independent manuscripts. The fourth chapter of the dissertation is a summary, conclusions, and a discussion of future directions in research about sleep, physical activity, obesity, and health implications of SDB.

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Chapter 1

Sleep Measurement and Monitoring in Children with Down Syndrome: A Review of the Literature, 1960-2012

Sleep measurement and monitoring in children with Down syndrome: A review of the literature, 1960-2012

Abstract

Children with Down syndrome (DS) are at risk for sleep disturbances due to the anatomical features of the syndrome. Over the past 50 years research studies have measured sleep in children with DS to characterize sleep architecture and its relation to developmental delay. In the 1980s sleep disordered breathing (SDB) was recognized as a major cause of sleep disturbance in DS. The aim of this comprehensive review is to synthesize studies and present the historical context of evolving technologies, methodologies, and knowledge about SDB and DS. Future research opportunities and practice implications are discussed.

Objective

Published accounts of sleep research in Down syndrome (DS) have appeared in the literature since the 1960s. The purpose and methodologies of the studies have been diverse, each contributing differently to the current state of the science on sleep in DS. The goal of this manuscript is to provide a comprehensive critical review and synthesis of research findings about sleep and its characteristics in children with DS, including the historical and methodological contexts, from the 1960s through 2012. A brief epidemiologic review of DS and its related clinical characteristics, a historical timeline of identification of DS, general technological developments in sleep measurement, and recognition of sleep disordered breathing (SDB) as an important health concern, provides context for the reviewed studies.

Introduction

Epidemiology of Down syndrome

Approximately 5,400 of the four million infants born in the United States (US) each year have DS. In recent years the rate of live births with DS has increased in the US, from ~1 in 1,100 in 1979 to ~1 in 850 in 2003 (1). The prevalence of DS varies between 1/650 and 1/1,000 worldwide (2-4). DS is the most common genetic cause of significant intellectual disability (5). DS affects the entire human population equally and is not dependent on geography, race, ethnicity, or socioeconomic standing (4). The prevalence of DS varies due to the interplay of a number of factors including changing trends in average maternal age, personal and religious views about intentional pregnancy terminations, as well as health care policy and national legislation leading to improved maternal health and prenatal care (6). Environmental factors such as smoking, alcohol consumption, fertility drugs, and contraceptives have not been shown to be significantly associated with increased risk of DS (3). Increased maternal age is the only known risk factor associated with DS, yet most children with DS are born to younger women because of higher general birth rates in this group (2).

In early childhood, children with DS generally have delayed development of speech and fine and gross motor skills. In the developed world, early intervention programs address the needs of children with DS and other types of developmental delay (DD) with relatively good success (7). Because of life-saving advances in health care, such as pediatric cardiac surgery and improved societal accommodations, children with DS are living longer and healthier lives (2, 8). In the first half of the 20th century, life expectancy was the early teenage years, and children were often institutionalized. Currently average life expectancy is close to 60 years (Appendix 1.A); and in the developed world, almost all children with DS live in the community in a home environment (9). Thus, it has become increasingly important to optimize the health of children with DS through preventive measures to avoid secondary complications and set the stage for a healthier adulthood. This review will provide background information for researchers interested in improving the sleep of children with DS as one avenue for improved overall health.

Clinical characteristics of DS and relation to sleep

The phenotypic characteristics of DS include DD, short stature, flat nasal bridge and oblique eye fissures. These characteristics were first described by John Langdon Down in 1866 (10), after whom the syndrome is named. In 1959, the etiology of DS was found to be an extra copy of chromosome 21 (11-13); thus DS is also referred to as Trisomy 21. Chromosome 21 is one of the most studied human chromosomes. It has been fully sequenced (5), yet the functions of many genes on the chromosome remain unknown, and the mechanisms by which the trisomy leads to the phenotypes of DS are unclear (14). DS is typically diagnosed prenatally or at birth. There are several clinical features of DS that potentially lead to disturbed sleep and/or increased risk for SDB. However, not all of these clinical characteristics are present in every child, and when present, vary in intensity. Hypotonia, relative macroglossia stemming from a normal size tongue not having enough room within a smaller size pharynx because of maxillary hypoplasia (15), small upper airway and underdeveloped midface (midfacial hypoplasia) are some of the physical features that may interfere with breathing during sleep and increase the risk of SDB (16). Additional SDB-predisposing characteristics in DS include crowding of the pharynx by a posteriorly-placed tongue, lymphoid hyperplasia (increased amount of tissue), reduction in pharyngeal muscle tone, and overweight (17). Children with DS are also at increased risk for congenital heart disease, pulmonary hypertension, leukemia, ear infections and scoliosis (6), all comorbidities potentially associated with disrupted sleep. In light of the increased risk for SDB in DS, and the importance of nocturnal sleep in cognitive development, behavior and daytime function (18, 19), it is important to understand sleep architecture and the nature of sleep problems in children with DS in order to design preventative or supportive interventions to maximize the benefits of sleep in the population. This review synthesizes the work completed through 2012 in pediatric DS sleep research.

Methods

Style and selection criteria of review

This review employs an inclusive methodology and narrative style to comprehensively examine previous accomplishments of sleep research in children with DS. As such it differs from a traditional quantitative systematic review which would focus on a well-defined question, narrowly focused on selective research with conforming measures. Because previous sleep research in children with DS asked diverse questions, implemented a variety of methodologies and standardized sleep monitoring and scoring standards were not used consistently (20, 21), there are few studies appropriate for a quantitative systematic review. The key words "Down syndrome," "Down's syndrome," "Trisomy 21," "Mongolism," "Mongloid," [DS was previously referred to as "Mongolism" through the 1970s] each in combination with "sleep," were used in searches of PubMed, Cumulative Index to Nursing and Allied Health Literature (CINAHL), Cochrane Library, Academic Search Complete, and Education Resources Information Center (ERIC). The searches were limited to articles published in English and in human subjects. Studies that included adults or mixed age groups of adults and children (22-25), daytime polysomnography and no nocturnal sleep measures (26, 27) were excluded. Single case reviews, editorials, and letters were reviewed for context. Twenty-seven studies of nocturnal sleep in children with DS, ages 0-21 years, were found and included in this review. Twenty-three of the studies included overnight polysomnography (PSG) and were summarized in tabular format by chronological order, Table 1.1 (28-50). The remaining four studies were parent reports (51-54).

Categories of studies and chronological order

Studies of sleep in DS are categorized as: 1) basic research describing sleep, 2) applied research of sleep in association with medical problems, and 3) holistic research with an ecological view of health, including the social and medical context of comorbidities associated with sleep problems. A majority of the studies in this review fall into at least two of these categories. Most applied and holistic studies in DS sleep research involve obstructive sleep apnea (OSA), a general group of disorders further grouped under a category referred to as SDB. Although there is overlap in categories of studies, there is a temporal sequence in that typically basic research precedes applied research which is followed by holistic research. During the 20th century technological advancements and new scientific knowledge paved the way for advanced basic research and applied research aimed at improving medical outcomes in children with DS. A summary of this historical context of sleep research in relationship with DS is presented in Table 1.2.

Findings

Basic research – measurement of sleep architecture in relation to intellectual disability

The first studies of sleep in DS described normal and abnormal sleep architecture. In basic research, DS presented a homogeneous group with respect to etiology of DD, with well-defined physical characteristics and was considered representative of DD (28, 29, 31, 34). Studies reported 3 to 5 sleep cycles alternating between nonrapid eye movement (NREM) sleep and rapid eye movement (REM) sleep. REM sleep had been discovered in the early 1950s, and since the 1960s a link had been observed between REM density and learning and mental function and disorders (55, 56); thus REM sleep was a new and intriguing topic of study. The relation between sleep and learning has long been of scientific interest. In particular, studies in the 1960s and 1970s found associations between the amount of REM sleep and memory processing (57, 58). Investigators were interested in discovering whether conditions associated with DD might be associated with a reduced amount or a lack of REM sleep. The first US polysomnographic study of children with DS compared the amount of REM sleep time between a group of boys with severe (n=5) and moderate (n=5) DD (28). The average amount of REM sleep over 3 study nights was 59 min in the "severe" DD group compared to 93 min in the "moderate" DD group. A Japanese study compared differences in total sleep time (TST), percentage of time in each sleep stage, REM density, and number of stage shifts, night awakenings, and body movements among children with DS (n=10), children with other types of developmental delay (OTDD) (n=10), and typically-developing (TD) children (n=8) (29). TST, percentage of time in each sleep stage, number of stage shifts, night awakenings and body movements did not differ among the groups. However, DD severity was associated with lower REM density (11.5% vs. 8.5% in more severe DD, measured by IQ). The average number of stage shifts per minute was 0.08 ± 0.02 and the number of night awakenings was 2 ± 2 in DS which was comparable to both TD and OTDD, (0.1 ± 0.03 and 5 ± 4, respectively). The REM amount of TST was 17 ± 4% for DS, 16 ± 6% for OTDD, and 20 ± 7% for TD. The proportion of TST designated as "indetermined sleep," was 4 ± 4% in DS, 2 ± 3% in OTDD, and 1 ± 2% in TD. Several studies examined the effects of pharmacological agents on sleep and daytime function in DS (30-32, 59). Petre-Quadens and de Greef (59) and Petre-Quadens and de Lee (30) reported on the effects of 5-hydroxytryptophan (5-HTP) on "quiet" (non-REM) and "paradoxical" (REM) sleep in children with DS. Based on earlier findings by Bazelon et al. (60), who observed improvements in hypotonia, 5-HTP was administered to children with DS in a quasiexperimental study. Authors observed REM sleep density increases comparable to TD children, however noted this was a temporary effect and did not influence later development (30). Grubar et al. and Gigli et al. (31, 32) examined the effect of butoctamide hydrogen succinate (BAHS) in children with DS. Based on Jackson's 1932 theory on the relation between cognitive deficits and sleep (61), these two studies used BAHS, a type of hypnotic drug, to increase the minutes of REM sleep in children with DS. In addition to BAHS, two 6-hour [undescribed] intensive didactic sessions (IDS) were administered as an intervention to increase REM sleep (32). Neither intervention increased the percent time of REM sleep. However, TST was significantly lower in the intervention with IDS (532 min vs. 564 min, $p < 0.05$).

Basic sleep research has continued through the 1980s to 2000s. Measures of arousal in various DD phenotypes (e.g., DS, fragile X syndrome) in relation to learning and memory were examined (34, 45). Miano et al. (45) examined NREM cyclic alternating patterns in association with learning in DS ($n = 9$), fragile X syndrome (FXS) ($n = 14$), and age-matched TD controls. Those with DS had lower sleep efficiency, higher percentage of wake after sleep onset (WASO), and reduced percentage of stage 2 NREM sleep compared to the other groups. Compared to TD, children with DS and FXS showed a lower percentage of A1 and higher percentages of A2 and A3 stages.

Three studies focused on cardiac response and heart rate variability immediately following apnea events among children with DS (36, 46, 50). Compared to controls with sleep apnea but without DS, children with DS exhibited a delayed cardio-respiratory response to apneas, which may suggest possible autonomic and brainstem dysfunction, causing slow recovery from an apnea. Delayed recovery from apnea events, and delayed resumption of ventilation, may put children with DS at increased risk for cardiovascular complications and pulmonary hypertension (50).

Applied research – measurement of obstructive sleep apnea, its prevalence and characteristics

Between 1980 and 1982, several editorials addressed the predisposition of children with DS to OSA because of physical features that place children at risk for airway obstruction during Sleep (62-65). It was proposed that the onset of OSA may not be in early infancy, but rather arise later with the development of lymphoid hyperplasia between one and four years of age. Several PSG studies that examined OSA prevalence in DS clinical populations (33, 39, 42-44, 47, 49), referred for snoring, sleep concerns, or other health problems, reported a higher prevalence of OSA, ranging from 54% to over 90%, compared to 1-4% of the typically developing and otherwise healthy children (19). By the time OSA was recognized as a concern in DS, methodologies to measure PSG-derived OSA diagnosis were established with standard PSG monitoring. Electrocardiograms (ECG) and oximetry were integral to PSG; however many of the studies were retrospective case reviews, and the measurement methodologies varied by clinic and/or hospital. Although most studies defined OSA based on apnea-hypopnea index (AHI), definition of AHI differed across studies. For example, a respiratory event could be defined as absent or reduced airflow of “at least 5 seconds” (38), “over 2 breath cycles” (47, 49), or as “2 [events] per hour” or “> 3 [events] per hour of TST” (39, 40). Although AHI measurements and scoring may seem similar, the prevalence rates within the clinical studies may vary due to differences in AHI definitions (66). Recently the AASM has reached consensus in defining AHI in pediatric populations (20, 21). A description of respiratory rules for scoring obstructive events, which has been adopted by the AASM, can be found in Appendix 1.B.

Studies of OSA in DS using non-clinical community samples report prevalence rates between 24% and 59% (35, 38, 42). Although each of these studies used different thresholds for defining OSA, the two community samples with higher level of participation, Dahlvquist et al. and Stebbens et al., showed lower prevalence of OSA, 24% and 31% respectively, compared to studies with referred samples (over 54%) (33, 39, 42-44, 47, 49).

Applied research – clinic-based research studies that evaluated treatment of OSA

A few studies have examined the effects of surgical interventions and the use of continuous positive airway pressure (CPAP) for OSA in DS. There exist no clinical trials evaluating these interventions for sleep improvement in DS. Two retrospective case reviews focused on measuring sleep before and after surgical intervention, CPAP, or position therapy intervention for correction of OSA (47, 48). Both studies documented improvements in OSA as a result of varied treatments. Rosen reported spontaneous resolution of OSA in 3 of 6 infants with DS after several months of using CPAP, indicating that OSA in infants with DS can be a transient phenomenon (47). Shete and colleagues reported improvements in sleep efficiency and AHI in children with and without DS who underwent adenotonsillectomy, although children without DS had greater improvements (48). Children with DS had pre-operative AHI and REM-AHI of 15 and 31, which decreased to 9 and 22 postoperatively. Pre-surgery, children without DS had AHI and REMAHI of 21 and 33 respectively, which were lowered to 2 and 6 post-operatively. Of note, 60% of children with DS had various comorbidities such as congenital heart disease and lung disease which affect breathing regardless of adenotonsillectomy. Among children with DS 73% needed additional intervention, such as CPAP, after surgery (48).

Holistic research – studies that look at the overall health and comorbidities

Some studies have examined a broad holistic view of sleep problems in children with DS (46-49). Comorbidities such as congenital heart disease, pulmonary hypertension, and obesity in children with DS present challenges in treating sleep problems and disorders. O'Driscoll et al. reported reduced cardiovascular and ventilator responses exacerbate acute hypoxic exposure in DS (46, 50). Several studies examined obesity in relation to OSA in children with DS, with inconsistent findings (38-40, 44, 48, 49). Fitzgerald and colleagues found no association between body mass index (BMI) and OSA in a clinical sample of 33 children with DS, age 0.2-19 years, who snored. Obesity was determined based on DS growth charts which allow for higher weight for stature than do growth charts for TD children. Fitzgerald reported 9% of participants met the criteria for obesity based on DS-specific weight for height charts (44). Shires et al. conducted a retrospective case review of 52 children with DS who had PSG, and found an association between OSA and increased BMI, which increased with age. Obesity was assessed using both DS and normal growth charts (49).

Parent report studies

In four questionnaire studies parents reported on symptoms suggestive of sleep disorders (51-54). Carter et al. conducted a community prevalence study of sleep problems in DS using the Children's Sleep Habits Questionnaire (CSHQ) and found that compared to parents of TD children, parents of children with DS reported more bedtime resistance (25%), not falling asleep in own bed (33%), restlessness during sleep (58%), night wakings (40%), daytime tiredness (70%), and bedwetting (26%) (52). Cotton and Richdale examined parental perceptions of the night time sleep in children with DS, autism, Prader-Willi syndrome (PWS) and TD children. Children with DS had more sleep problems than TD children, but fewer sleep problems than those with autism or PWS (51). Another study conducted in the same year, 2006, measured sleep by both parent report and PSG, reported a discrepancy between parent reports and PSG results in children with DS. Of children who had abnormal PSGs only 34% had corresponding parent report of sleep problems (43). A recent parent report study by Rosen et al. (53), using an anonymous Internet survey of a clinical population, found that 47% of parents reported witnessed apneas following adenotonsillectomy, underscoring the need for continued monitoring for OSA after surgical intervention. Breslin and colleagues conducted a questionnaire study, using the CSHQ in parents of 35 children with DS, age 7-18 years (54). The results were consistent with Carter et al. (52), showing widespread sleep problems ranging from falling asleep in a parent or sibling's bed (29%), to having at least one symptom of sleep disordered breathing, including loud snoring, cessation of breathing, and gasping or snorting (60%) (54).

Discussion

In examining sleep in children with DS, it is important to consider the measurement of sleep in the context of advancing technology, varying research methodologies and research ethics, changing attitudes about DS, and different cultural and geographic settings. Some of the research studies in this review, though probably conforming to the standards of the day, would not be acceptable in today's regulatory and ethical environment.

Often early studies did not specify recruitment methods and were performed on institutionalized individuals likely without written consent of parents. In the 1960s and 1970s, research on institutionalized and/or those with DD, was not regulated as it is currently, after the 1979 Belmont report (67). The 1970s and 1980s saw an increase in de-institutionalization in the developed world (9) as more parents opted to raise their children with DS at home. In the 1980s studies included institutionalized subjects (31, 32), however parent consent was mentioned explicitly in some studies during the late 1980s and early 1990s (35). Gigli et al. described for the first time the environment of the laboratory as a quiet, partially soundproofed, shielded laboratory within the institution, where children came with familiar assistants who stayed with them until they fell asleep (32).

In 1987, Southall and colleagues published the first study that evaluated OSA with PSG in children with DS (33). Though considered a landmark study, like most early studies, the sample was small and biased due to pulmonary vascular disease present in the children. Like Southall et al., most studies used clinical populations with comorbidities that are challenging to interpret due to confounding factors. Furthermore, in most studies, the number of subjects was inadequate for statistical evaluation and generalizability was limited. PSG is a costly and inconvenient method regardless of the presence of DS. Therefore PSG studies typically do not have a large number of participants. Nevertheless, these studies provide valuable information to build upon.

The measurement of sleep in children with DS evolved through advancing technology and consensus on sleep measurement. Early studies focused more on understanding sleep patterns in a homogeneous population with intellectual disability. Later studies sought to measure the prevalence of sleep problems and disorders and ways to resolve them. Only in recent years has the importance of chronologic age to sleep patterning received attention (19), thus some early studies tended to lump wide age groups of children with DS into single studies. Indeed a widely cited DS pediatric sleep study included an age-range of 0-50 years (24). The study was excluded from the current review because it was impossible to articulate the pediatric implications. As the field of pediatric sleep becomes more refined it is imperative for future research measuring sleep in DS to use standardized methods such as those described by Accardo et al. and Grigg-Damberger et al. (20, 21). For example, authors need to specify the environment of measurement and whether a parent accompanied the child. Such descriptions were absent from a majority of the papers reviewed in this report. Most studies did not specify a classification of OSA as mild, moderate or severe, and results were based on the average of a wide range of characteristics. The presence or absence of OSA was measured using different standards among these studies. Studies that evaluate the effectiveness of surgical interventions would benefit from a standard diagnosis and severity measurement (41, 47, 48). It is important to know whether an intervention at least partially resolves OSA, rather than only complete resolution. Furthermore, the confounders of ear and upper respiratory infections, tonsils presence/size, heart and lung issues, hypertension, and other factors known to affect sleep or breathing during sleep, need proper assessment and reporting within studies. Few studies have addressed the role of obesity in DS and its association with sleep problems (68). One study that found no association between obesity and OSA used a clinical population, 91% of whom were not considered obese based on DS growth charts (44). DS-specific charts classify a smaller proportion of children as obese compared to Center for Disease Control (CDC) growth charts for TD children (69). It is unknown what proportion would have been considered obese based on these CDC growth charts. In contrast, another study used both DS and normal growth charts and found an association between obesity and OSA in DS, using either of the standards (49).

Given the morphological features of DS that are conducive to OSA, it seems important to consider using obesity standards based on TD growth charts. Why not hold children with DS to the same standards for obesity as the general population of children, especially given our current awareness of obesity association with poor sleep and related unhealthy outcomes? As the population of children with DS is expected to live decades longer than previous generations, it is important to raise the expectations of adequate sleep and overall health outcomes as with any other population of children. It is important to teach healthy sleep, activity, and eating habits at an early age so that these habits and behaviors can become health promoting routines carried into adulthood. Early healthy sleep habits and routines are critical for all children, but may be even more critical in children with DS due to the underlying disease mechanisms and comorbidities. Modifiable environmental factors, such as exposure to tobacco smoke, also need to be considered as part of a comprehensive preventive plan (70).

In prevalence studies (34, 37, 42) with families, information about reasons for low response rates would be useful to interpret generalizability and address future recruitment issues in communities. Potential reasons for low response could be perception of no sleep problems as reported by Shott et al. (43); perception that if there is a problem there would not be an easy solution because the child would refuse the most common treatment, CPAP; unwillingness of parents to put the child through a night of laboratory measurement; or, in a child with prior tonsillectomy, the parent may believe sleep problems have been resolved to the extent possible.

Few studies highlight the importance of universal and frequent assessment of sleep problems in children with DS, not only for diagnosis but also for assessing improvement with or without treatment (43, 47). One study discussed the potential negative unintended consequences of treatment such as the concern of worsening midface hypoplasia secondary to wearing a CPAP interface for longer than necessary (47). These issues are essential to promoting improvements in sleep of children with DS.

Conclusions

Recent studies emphasize the importance of childhood determinants of health in adulthood (71). Because of the longer life expectancy in children with DS, it is important to maximize comprehensive health in childhood to build a foundation for adult health. Optimal sleep is essential for health, yet to date, studies consistently report sleep concerns in children with DS. Many studies lack a theoretical framework to explain the overall picture of sleep problems in children with DS. Prior studies have used clinical populations likely to experience sleep problems. Some have treated subjects as individual cases, reporting individual outcomes, and have used varying methodologies. More systematic research on sleep problems and intervention in children with DS is warranted.

Limitations of this review

This review included only English language literature up to December 2012. The type of PSG equipment was not a consideration in this narrative review because although some authors reported their equipment specifications, many did not, and when addressed it varied from study to study. Calibration of equipment was not discussed in this review because it was rarely addressed in the publications, yet it is well known that calibration problems can introduce bias in measurements.

Practice points

1) The patterning of sleep in children with DS has interested researchers for years because of the perceived relation of sleep with intellectual ability.
2) Characterizing and understanding the nature of sleep problems in children with DS is an essential element in prevention of secondary conditions in children with DS. Children with DS have a longer life expectancy than in the past; it is important to maximize health.

3) Sleep disordered breathing, specifically OSA, is recognized as a major sleep problem in children with DS. Assessing the size of tonsils has a major role in addressing this problem. Tonsillectomy resolves 30-50% of OSA in DS.

4) Practitioners are advised to screen for sleep disorders in children with DS despite a lack of history of snoring. Regular sleep assessments after tonsil/adenoid surgery are recommended.

Research agenda

1) Assess the reliability of diagnostic monitoring such as overnight oxygen monitoring, or actigraphy in child's home.

2) Incorporate actigraphy for assessment of sleep, and other home measures, over days, in all age groups, compare child and family patterns.

3) Measure the overall environment of the child to assess sleep problems. Consider home environment, the role of TV, lights, noise in the house and neighborhood, etc.

4) Trial sleep position therapy for OSA.

5) Trial early intervention to determine if it improves outcomes. For example, would early preschool CPAP use increase child acceptance?

6) Complete longitudinal studies to depict the history of sleep apnea in DS with treatment. How does it change as the person grows?

7) Basic research in REM sleep of children with DS who do not have OSA. This is important since most early studies did not specify OSA as a consideration and OSA was a confounder in later studies.

8) Surgery corrects 30-50% of cases of sleep apnea in DS, but what about severity levels? Does surgery reduce severity in cases not completely resolved? Conduct systematic studies to assess severity before and after various treatments.

9) Include qualitative studies and future quantitative studies about attitudes of parents toward sleep and obesity – should children with DS be held up to normal standards of obesity?

10) Incorporate Tanner staging, hormone levels, and circadian rhythms in studies of relation of sleep problems to obesity in DS.

11) Examine the extent to which the severity of OSA can be reduced by just reducing obesity.

12) Conduct studies to determine the role passive smoking plays in associations between DS and OSA.

13) Conduct genetic studies — understanding chromosome 21 genes and why some are protective and some promote illness?

14) In light of the importance of chronologic age to sleep patterning in children, using narrow age groups may help characterize sleep problems more specifically in children with DS.

15) Many research studies in the past did not specify consent circumstances, nor did they describe the laboratory conditions. These circumstances need to be clearly stated in future research.

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Table 1.1. Studies of nocturnal sleep measurement with polysomnography/polygraphy in children with Down syndrome 1969-2012

Author, Year, Location	Sample N Gender, Age	Sample Inclusion /Exclusion	Design (D) Objective (O)	PSG / PG N, D, U	Sleep & Other Measures	Findings
Castaldo [28] *1969* *U.S.A.*	DS: 10 boys 12-16 yrs	Institutionalized, normal clinical EEG, not on medications; 2 groups of 5, moderate and severe DD	D: cross-sectional age-matched comparison O: level of DD correlated with REM duration	N: 4 consecutive D: overnight U: nights 2-4	EEG, EOG, EMG D & K criteria, Sleep and REM Duration Stanford-Binet IQ	Once in bed no difficulty falling asleep. Lower sleep and REM duration in the severe DD group. No statistical significance.
Fukuma et al. [29] *1974* *Japan*	DS: 5 boys, 5 girls 7-17 yrs Non-DS DD group: 5 boys, 5 girls 7-17 yrs Normal: 8 boys,2 girls 8-15 yrs	DS & DD groups institutionalized; Normal group living at home	D: 3 group Cross-sectional comparison O: Determine correlation of REM with level of intellectual ability	DS & DD groups: N: 3 with 7-day intervals U: 2-3 Normal: N: 2 with 7-day interval U: 2	EEG EMG EOG R & K criteria TST, REM, % sleep stage, stage shifts/min, NW/night, body movements Suzuki-Binet IQ	DS & DD groups mostly in stages 1 and 2; both had longer TST than normal group. DS had higher minutes of time that could not be assessed (indetermined sleep) and greater number of body movements. Lower sleep stage shifts and awakenings in DS. No statistical significance.
Petre-Quadens & De Lee [30] *1975* *Belgium*	DS: 9 neonates, 6 with PSG. Control: 14 normal neonates 11 small-for-date neonates. GNS	Unknown criteria, 2 of the infants with DS were cared for by parents.	D: longitudinal, started 5HTP between 2 and 6 months, continued administration for 12-36 months O: effect of 5-HTP on REM sleep and sleep duration	N: 4-19 with unknown intervals D: overnight U: unknown	EEG EOG EMG	Short lasting effect of 5-HTP on increasing REM sleep, muscle tone and improvement of motor behavior in neonates with DS. Abnormal development of sleep spindles likely incompatible with learning. No statistical significance.

Table 1.1. Continued

Author, Year, Location	Sample N Gender, Age	Sample Inclusion /Exclusion	Design (D) Objective (O)	PSG / PG N, D, U	Sleep & Other Measures	Findings
Grubar et al. [31] *1986* *Italy*	DS: 8 boys 8.11±2 yrs	Institutionalized, DS confirmed by karyotyping, drug-free for at least 2 months, free of medical problems known to affect sleep	D: Experimental, pre-post administration of 600 mg BAHS. O: Is BAHS associated with increased REM time in DD?	N: 7 consecutive D: overnight U: 2-7 2 & 3 were baseline, 4 & 5 BAHS, 6 & 7 No BAHS	EEG, EOG,EMG Stage % times TST, REM REM latency NW, WASO R & K criteria IQ	7 out of 8 subjects with DS increased their REM time. One who did not have an increase had the highest REM at baseline within normal range, indicating a homeostatic limit in REM variation. No side effects were observed.
Gigli et al. [32] *1987* *Italy*	DS: 5 boys 9.5±2.7 yrs	Institutionalized, DS confirmed by karyotyping, drug-free for at least 2 months, free of medical problems known to affect sleep	D: Experimental Compare baseline, BAHS, and BAHS+6 hrs intensive didactic program the following morning. O: Does BAHS+ intensive learning increase REM?	N: 12 nights over a 30-day period. D: overnight U: 2-12	EEG, EOG, EMG Stage % times TST, REM REM latency NW, WASO R & K criteria R, IQ	BAHS alone increased % of REM. BAHS + 6 hours of intensive learning was associated with reduced TST, increased WASO, increased stage 1 sleep; REM sleep stayed the same, improve R. Complete rebound to baseline after cessation of BAHS + intensive learning. No side effects were observed.
Southall et al. [33] *1987* *England*	DS: 12 1 mo to 6 yrs Controls: 20 Age-matched to children with DS GNS	DS: 4 recruited from community, 8 recruited after admission to hospital for congenital heart disease and pulmonary hypertention. Controls: random community	D: cross-sectional pilot study comparison at baseline between DS & controls, blinded analysis; pre-post comparison for treatment of OSA O: Prevalence of OSA; effectiveness of treatment for OSA	N: 2 D: overnight (7±2.6 hours) U: 2 Setting: DS, 10 in hospital, 2 at home. Control: all at home.	SaO_2, expired CO_2 respiratory abdominal movement	50%, of the mostly clinical population with DS (n=6), had OSA. All OSA cases had abnormal inspiratory resistance and elevated end-tidal CO_2; all but one had hypoxaemia. Treatment with different strategies, depending on patient, ranged from postural changes to adeno-tonsillectomy. Post treatment there was slight improvement, to complete recovery, with regression in one patient.

Table 1.1. Continued

Author, Year, Location	Sample N Gender, Age	Sample Inclusion /Exclusion	Design (D) Objective (O)	PSG / PG N, D, U	Sleep & Other Measures	Findings
Hamaguchi et al. [34] *1989* *Japan*	DS: 6 boys 4 girls 9 mo to 7 yrs Control: 4 boys 12 girls 5 mo to 8 yrs	DS: Unknown if community or institutionalized No congenital heart disease	Cross-sectional comparison of sleep parameter in DS and control O: description of sleep stages and REM in young children with DS	N: 1 D: 326-564 min U: 1	EEG, EOG, EMG, ECG, spirograms, % of sleep stages, REM, REM Intervals, R, NW, body movements, twitches. R & K criteria Tsumori-Inage DQ developmental level	2 children with DS had higher REM % and R than controls. 4 children with DS had more body movements than controls. 5 cases showed abnormal patterns of body movements. Fewer twitches in children with DS than controls. No statistical significance.
Stebbens et al. [35] *1991* *England*	DS: 20 boys, 12 girls 0-9 yrs Control: 15 boys, 11 girls 0-6 yrs	Community; response rate: 94%, all with PSG. One had adenoidectomy, one had UAO as neonate, 12 had congenital heart disease, 12 had other structural defects. Control: random	Case-control comparison of UAO, blinded analysis of sleep measures O: Prevalence of UOA by parent and clinical assessment	N: 1, 2 in children under 2 yrs D: 12 hours U: 1 & 2	OSA episode = airflow cessation of at least 4 sec. Pulse oximetry: SaO_2, chest movements, end-tidal CO_2 nostril concentration, clinical assessment. Parent questionnaire: presence of 6 clinical symptoms.	31% of children with DS vs. 4% of control had symptoms of UOA. 41% had increased inspiratory resistance in DS, vs. 3% in control. Increased incidence of stridor in DS. Site of UOA varied. Statistically significant differences between DS and control in episodic oxygen desaturation. Reports on individual cases. 28% of DS cohort eventually had adenotonsillectomy.
Ferri et al. [36] *1998* *Italy*	DS: 7, GNS 8.6-16.5 yrs Control: 6, GNS 8-17.5 yrs	Unknown recruitment. DS: karyotyping, no respiratory illness, no obesity, no abnormal upper airway, no severe macroglossia, no AAI. 2 had heart abnormalities	D: Case control comparison of HRV & sleep parameters O: is the heart overburdened by sleep difficulties?	N: 2 nights in lab, but recorded 2nd night only D: overnight U: 1 on second night	Heart rate Sleep structure: stages, stage shifts, WASO, REM latency, NW, TST, SEI, SOL R& K criteria Central and obstructive AHI/hr	Could not stage sleep in all participants, children with DS had reduced HF and increased low-frequency heart rate. Brainstem involvement in central apneas in DS.

Table 1.1. Continued

Author, Year, Location	Sample N Gender, Age	Sample Inclusion /Exclusion	Design (D) Objective (O)	PSG / PG N, D, U	Sleep & Other Measures	Findings
Levanon et al. [37] *1999* *Israel*	DS: 23, 1-10 yrs GNS Control : 13, 1-10 yrs GNS	DS: Referral by family physician or outpatient genetic clinic. Control: Children referred for snoring but were not found to have OSA	D: Cross-sectional comparison O: Characteristics of sleep disorders in DS, respiratory disturbance, arousals, awakenings & movements	N: 1 D: overnight, 6-8 hrs U: 1 Clinic setting	RDI = apnea+ hypopnea index; Arousal / awakening index; Leg movements R & K criteria	Time in each stage of sleep not different from control. RDI significantly higher in DS. More awakenings and arousals.
Dahlqvist et al. [38] *2003* *Sweden*	DS: 21, 17 with PSG 2-10 yrs GNS Controls: 21 normal siblings GNS	Community; all families with DS in one city were invited. 75% response rate 61% success with PSG. Control : Siblings	D: Cross-sectional comparison O: Prevalence of OSA	N: 1 D: overnight U: 1 Clinic setting	Obstructive Apnea episode=airflow cessation of at least 5 sec., AHI, TST, snoring, sleep position changes, BMI	24% OSA prevalence based on AHI>1. OSA is not related to DS; tonsils hyperthrophy and higher BMI, common in DS, are related to OSA. More position changes and snoring in DS. Shorter TST in DS.
de Miguel–Diez et al. [39] *2003* *Spain*	DS: 108 69 boys 39 girls 1-18 yrs	Patients referred to tertiary care hospital dept. of pulmonology.	D: cross-sectional descriptive O: Prevalence of OSA, association with obesity and age.	N: 1 D: overnight U: 1 Hospital setting	PG OSA= AHI≥ 3/hr BMI Tonsillar size	54% prevalence of OSA, boys and those ≤ 8 yrs old had greater risk. Observed no relation between BMI and OSA.
Dyken et al. [40] *2003* *U.S.A.*	DS: 9 boys 10 girls 3-18 yrs	Outpatient population	D: Descriptive pilot study O: Prevalence of OSA, association with age, obesity	N: 1 D: overnight U: 1 Clinic setting	SaO_2, EEG, ECG, EOG, EMG OSA= AHI >1	79% of clinic population had OSA. No central apneas. There was an association between OSA and obesity, older age, and poor sleep quality.

Table 1.1. Continued

Author, Year, Location	Sample N Gender, Age	Sample Inclusion /Exclusion	Design (D) Objective (O)	PSG / PG N, D, U	Sleep & Other Measures	Findings
Mitchell et al. [41] *2003* *U.S.A.*	DS: 23, 11 with PSG 13 boys 10 girls 1 day – 10.2 yrs	Children with DS referred to Otolaryngology dept. for UAO	D: Retrospective case review O: determine causes of upper airway obstruction in DS	N: 1 D: overnight U: 1 Hospital setting	PSG (no description of sleep parameters or AHI index) Reason for referral, diagnosis, surgical procedures, complications, comorbidities	11 children had OSA, most > 2 yrs. 73% of children with OSA had otitis media. 10 had laryngomalasia, 1 had inhaled a foreign body, 1 had tracheomalacia. Children without OSA were mostly < 2 yrs. Causes and severity of UAO are related to the age of child and comorbidities.
Ng et al. [42] *2006* *Hong Kong*	DS: 15 boys 7 girls Under 18 yrs Control: 15 boys 7 girls Under 18	Community sample, families from DS Association Control: Non-DS, referred to hospital for snoring. Excluded previous adeno-tonsillectomy.	D: Cross-sectional study. Age, gender, weight and height matched controls. O: Compare 1)prevalence of OSA in DS with Non-DS controls who snore; 2) characteristics of OSA vs. No OSA, 3) OSA in DS & Non-DS.	N: 1 D: overnight U: 1 Laboratory setting	S: Time asleep, arousal index, AHI, Desaturation index, SaO_2, during sleep, OSA= AHI> 1.5 BMI, asthma, tonsil size & hypertrophy.	6% response rate, therefore possibly self-selected for sleep problems. Prevalence of OSA in DS: 59%. Not all children with DS and OSA snore; nearly 40 percent of children with DS and OSA did not snore habitually.
Shott et al. [43] *2006* *U.S.A.*	DS: 63 56 with PSG Enrolled by age 2 yrs, followed for 5 yrs	Clinic population enrolled following otolaryngological problems	D: 5- year longitudinal prospective cohort O: Does parental questionnaire predict sleep problems in children?	N: 1 or more, not on consecutive nights D: overnight U: all Clinic setting	R & K criteria sleep duration; percentage of sleep time spent in different stages of sleep; number of arousals from sleep	Parent reports fall short of identifying all children with sleep problems. 54%-80% of children had abnormal PSGs. Of the abnormal PSGs only 34% of parents suspected problems. Therefore it is recommended that all children with DS have PSG at age 3-4 yrs regardless of history of snoring.

Table 1.1. Continued

Author, Year, Location	Sample N Gender, Age	Sample Inclusion /Exclusion	Design (D) Objective (O)	PSG / PG N, D, U	Sleep & Other Measures	Findings
Fitzgerald et al. [44] *2007* *Australia*	DS: 20 boys 13 girls 0.2-19 yrs	Children with DS who snored and had a PSG, in hospital setting. Exclude previous adeno-tonsillectomy or CPAP	D: Retrospective chart review O: Association of OSA with snoring. Should those who snore have a PSG routinely?	N: 1 D: overnight U: 1 Hospital setting	Sleep stages R & K criteria. Sleep efficiency, OSA= AHI>1; Hypopnea =airflow decrease of 20%-50% of baseline amplitude. Significant resp. event if lasted >2 resp. cycles & had ≥3% fall in SpO_2. Arousal index	91% were not obese (based on DS growth charts), yet 97% had OSA. Average O_2 desaturation was 4%; average AHI index was 12.1. Higher AHI was associated with higher number of arousals. Recommend PSG as a routine for children with DS who snore, regardless of obesity.
Miano et al. [45] *2008* *Italy*	DS: 8 boys, 1 girl 8-20 yrs Control: 14 fragile X 26 normal 30 males 10 females 7-26 yrs	Children attending an educational institute (DS and Fragile X). Normal controls from community in same region. Excluded obese and OSA.	D: Cross-sectional study. Age & gender matched controls. O: Manifestation of intellectual disability in relation to sleep architecture.	N: 2 D: overnight U: 2nd night Laboratory setting	Macro- and micro-structures including TIB, TST, sleep efficiency, cyclic altering pattern IQ	Lower sleep efficiency and reduced stage 2 NREM sleep in DS. Reduction in % of REM sleep is associated with intellectual disability
O'Driscoll et al. [46] *2010* *Australia*	DS: 4 boys, 6 girls Non-DS SDB: 6 boys, 4 girls Normal controls: 2 boys, 8 girls 3-17 yrs	Clinic based recruitment: DS & non-DS referred for SDB; Non-referred normal group	D: cross-sectional comparison of 3 groups. O: what is the HR response to arousal in different groups?	N: 1 D: overnight U: 1 Hospital setting	EEG, ECG, EOG, EMG; HR Arousals (ASDA guidelines); defined Defined mild OSA = 1-5 OAHI events per hr; moderate/severe OSA = >5 OAHI events per hour	No differences in 3groups with respect to demographics or BMI. No significant difference between groups in REM, NREM, sleep efficiency, no difference in baseline HR. HR response to arousal in REM and NREM was significantly lower in DS group.

Table 1.1. Continued

Author, Year, Location	Sample N Gender, Age	Sample Inclusion /Exclusion	Design (D) Objective (O)	PSG / PG N, D, U	Sleep & Other Measures	Findings
Rosen[47] *2010* *U.S.A.*	DS: 29 infants under 2 yrs GNS	All infants with DS who were referred to a children's hospital for sleep study over 5 yrs, 2004-2009	D: retrospective chart review, longitudinal follow-up O: effects of intervention; do infants with DS outgrow OSA spontaneously?	N: 1 or more D: overnight, >6 hrs U: all Hospital setting	EEG, ECG, EMG, EOG, R & K criteria / AASM after 2007. Event defined as chest and abdominal motion with reduction in airflow of ≥90% of baseline, lasting ≥ 2 breath cycles. OSA=AHI>1	16 of 29 were diagnosed with OSA. One treated with supplemental oxygen at night, 2 adenoidectomy, 4 adeno-tonsillectomy, 6 CPAP, 3 lost to follow-up. 50% of those treated with CPAP had spontaneous resolution of OSA. Recommend frequent assessment.
Shete et al.[48] *2010* *U.S.A.*	DS: 7 boys, 4 girls Mean age 8.5 yrs Non-DS: 8 boys, 1 girl Mean age 6.7 yrs	Sleep center patients, selected if had PSG-confirmed OSA defined: AHI>2, adenotonsillectomy, and follow-up PSG Excluded laryngomalacia, tracheomalacia	D: Restrospective chart review; pre/post-surgery comparison; O: examine if adeno-tonsillectomy improves AHI in children with DS	N: 2, pre & post surgery D: overnight U: 2 Hospital setting	EEG, ECG, EOG, EMG, Sleep efficiency AI; R & K criteria. SaO_2, oronasal airflow, REM and total AHI	BMI mean: DS 29.8 kg/m^2, non-DS 27.6 kg/m^2; 60% of DS group had comorbidities: congenital heart disease, lung disease & immune deficiency. Both DS and non-DS groups had improvements in total and REM AHI. Non-DS group had more improvements. DS group did not improve significantly in lowest SaO_2
Shires et al.[49] *2010* *U.S.A.*	DS: 52 28 boys, 24 girls 2-18 yrs	One pediatric hospital clinic patients over 10 yrs, 1995-2005	D: Retrospective Case review O: Is higher BMI associated with OSA in children with DS?	N: 1 D: overnight U: 1 Clinic setting	OSA=AHI>1 RDI ≥2 resp. events over 2 breath cycles & >3% fall in SaO_2. BMI, assessed obesity on both DS and standard growth charts	63% had OSA Children with OSA were significantly older and had higher BMI.

Table 1.1. Continued

Author, Year, Location	Sample N Gender, Age	Sample Inclusion /Exclusion	Design (D) Objective (O)	PSG / PG N, D, U	Sleep & Other Measures	Findings
O'Driscoll et al. [50] *2012* *Australia*	DS: 32 18 boys, 14 girls TD: 32 23 boys, 9 girls 2-17 yrs	All DS & TD children had been referred for investigation of SDB.	D: Cross-sectional comparison, age- & OAHI-matched O: Compared to TD, do children with DS have reduced cardiovascular response & delayed re-oxygenation after obstructive resp. events?	N: 1 D: overnight U: 1	EEG, ECG, EOG, EMG; scored resp. events $\geq$ 2 resp. cycles. OAHI= total N of obstructive apneas, mixed apneas, and obstructive hypopneas per hr of TST HR	Children with DS had significantly reduced HR changes post-event during NREM (DS: 21.4% $\pm$ 1.8%, TD: 26.6% $\pm$ 1.6%, change from late to post-event.) and delayed reoxygenation post event, indicating compromised acute cardio-respiratory response. Inefficient cardiorespiratory response to apnea may place children at risk for cardiovascular complications like pulmonary hypertension.

5-HTP: 5-hydroxytryptophan; AAI: Atlanto-axial instability; AASM: American Academy of Sleep Medicine; AHI: apnea/hypopnea index; AI: arousal index; ASDA: American Sleep Disorders Association; BAHS: butoctamide hydrogen succinate; BMI: body mass index; CPAP: continuous positive airway pressure; D: duration; D & K: Dement and Kleitman; DD: developmental delay; DQ: developmental quotient; ECG: electrocardiogram; EEG: electroencephalography; EMG: electromyography; EOG: electrooculography; GNS: gender not specified; HF: high frequency; HR: heart rate; hr: hours; HRV: heart rate variability; IQ: intelligence quotient; min: minutes; mo: month; N: number; NREM: non-rapid eye movement; NW: number of awakenings; OAHI: obstructive apnea hypopnea index; OSA: obstructive sleep apnea; PSG/PG: polysomnography/polygraphy; R: ratio of oculomotor frequencies; R & K: Rechtschaffen and Kales; RDI: respiratory disturbance index; REM: rapid eye movement; Resp: respiratory; SaO2: oxygen saturation; Sec: second; SEI: sleep efficiency index; SOL: sleep onset latency; TIB: time in bed; TST: total sleep time; U: used; UOA: upper airway obstruction; WASO: wake after sleep onset; yrs: years.

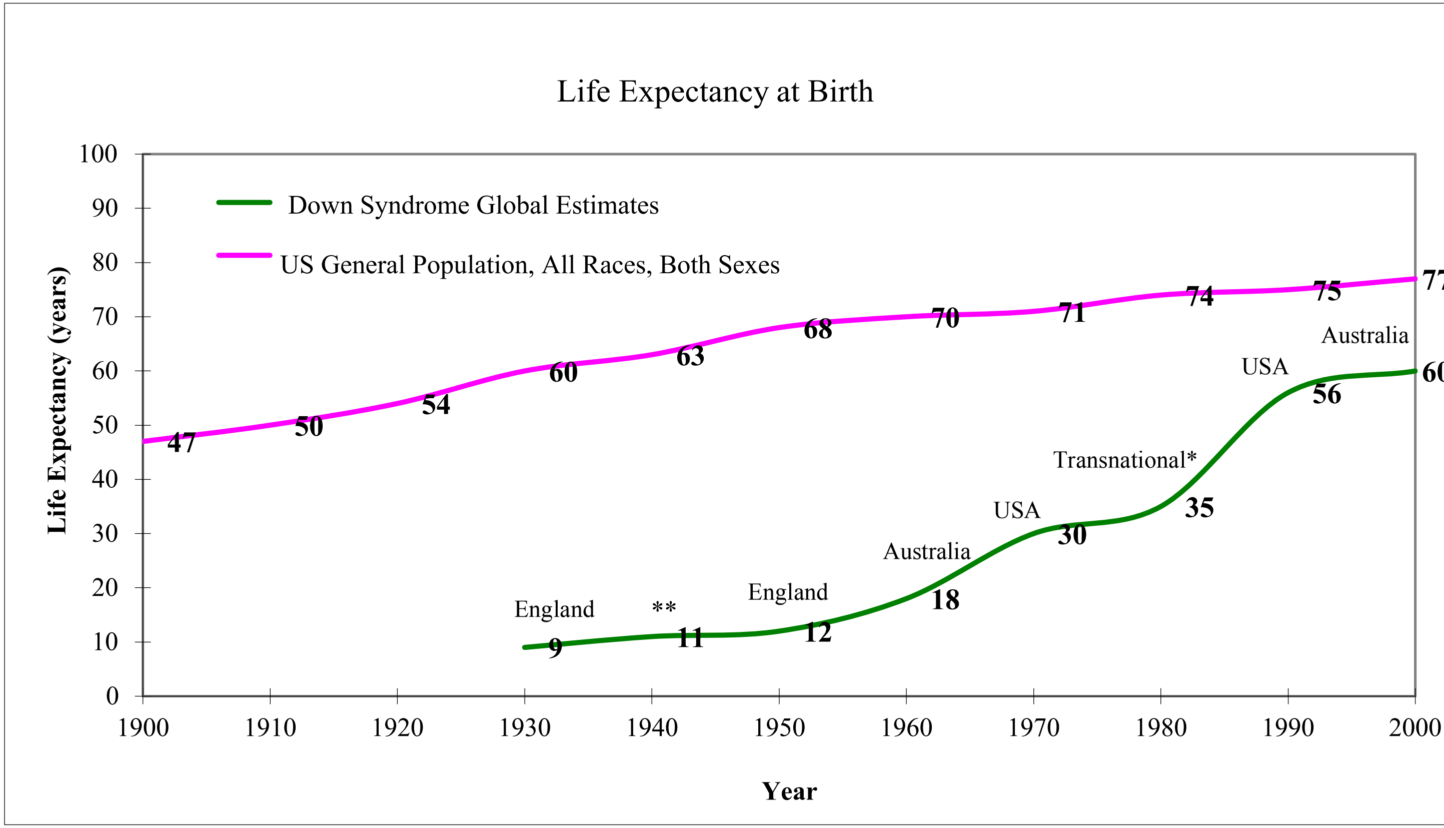
Table 1.2. Historical timeline of Down syndrome sleep research in the context of general sleep research.

Year(s)	***Event(s)***
1856	JL Down identified DS and its features as a distinct entity.[10]
1889	R Caton[73] & A Morrison[74] described symptoms of patients resembling what we know as "sleep apnea" today; then called "Pickwickians" after a sleepy character in an 1837 Dickens work referred to by Morrison. One of the characteristics of "Pickwickians" was the presence of overweight.
1924	First EEG, H Berger, published in 1929.[75]
1935	AL Loomis, EN Harvey and G Hobart showed EEG is vastly different at night.[76, 77]
1960-1962	First physiological recordings in sleeping Pickwickians, Heidelberg University[78] and National Institutes of Health in Bethesda.[79]
1966	Earliest sleep recordings involving children with DS by Jouvet and Petre-Quaden (in French).[80]
1967	Italian symposia "Bologna group" held first conference to attract sleep researchers—Cornerstone of "Sleep Medicine".[55]
1968	Rechtschaffen & Kales first standardization of criteria used by sleep laboratories to report human sleep scale data, generally used until 2007 until AASM manual was published.[81]
1969	First sleep recordings of children with DS in the U.S. by Castaldo (Kansas).[28]
1970	First sleep clinic opened in U.S. (Stanford).[55]
1970s	Lots of basic research in the function of sleep in general. Additional sleep studies of children with DS with primary interest in basic research in sleep staging and characteristics.
1974	Pulse oximetry was developed by Aoyagi and Kishi and was reported in publications in1975.[82]
Late 1970s	Airflow, respiratory indicators and peripheral pulse oximetry were added to polysomnography.
1977	First published use of term "Sleep apnoea Syndrome" by the "Stanford group" (Guilleminault & Dement) defined based on polysomnographic findings. Half the patients had hypertension, basis of bringing attention later to the cardiovascular disease connection with sleep apnea.[83]
1980s	Editorials on DS characteristics predisposing children with DS to Sleep apnea, e.g. Silverman.[17]
1987	First PSG study of OSA in DS by Southall.[33]
1993	T Young study published in NEJM, brought attention to sleep disordered breathing, and its consequences for the cardiovascular system, in the general population as a public health problem.[84]
2007	The AASM Manual for the Scoring of Sleep and Associated Events was published by the American Academy of Sleep Medicine.

AASM: American Academy of Sleep Medicine; DS: Down syndrome; EEG: electroencephalography; NEJM: New England Journal of Medicine; OSA: obstructive sleep apnea; PSG: polysomnography.

Appendix 1.A.

Life Expectancy of Individuals with Down Syndrome, Compared with Life Expectancy in U.S. General Population



Data sources:
http://www.cdc.gov/nchs/data/hus/hus05.pdf#027
Wattenberg BJ. The Statistical History of the United States, 1976
Bittles AH and Glasson EJ. Med Child Neurol. 2004 Apr;46(4):282-6.

* Australia, USA, Canada, Europe

** Extrapolated

Appendix 1.B.

Description of respiratory rules for scoring obstructive events Adopted by the American Academy of Sleep Medicine

	Pediatric	Adult
Obstructive apnea	• Drop in thermal sensor amplitude by ≥ 90% baseline • Duration ≥ 2 missed breaths • ≥ 90% duration meets amplitude reduction criteria • Continued or increased inspiratory effort during reduced airflow	• Drop in thermal sensor amplitude by ≥ 90% baseline • Duration ≥ 10 sec • ≥ 90% duration meets amplitude criteria • Continued or increased inspiratory effort during absent airflow
Central apnea	• Drop in thermal sensor amplitude by ≥ 90% baseline • **EITHER** duration ≥ 20 sec **OR** ≥ 2 missed breaths and associated with arousal, awakening or ≥ 3% desaturation • Absent inspiratory effort	• Drop in thermal sensor amplitude by ≥ 90% baseline • Duration ≥ 10 sec • ≥ 90% duration meets amplitude criteria • Absent inspiratory effort during absent airflow
Mixed apnea	• Drop in thermal sensor amplitude by ≥ 90% baseline • Duration ≥ 2 missed breaths • ≥ 90% duration meets amplitude reduction criteria • Absent inspiratory effort initially, then resumption of effort during latter part of event	• Drop in thermal sensor amplitude by ≥ 90% baseline • Duration ≥ 10 sec • ≥ 90% duration meets amplitude criteria • Absent inspiratory effort initially, then resumption of effort during latter part of event
Hypopnea	• Drop in nasal air pressure transducer amplitude by ≥ 30% • Duration ≥ 2 missed breaths • ≥ 90% of duration meets amplitude criteria • Associated with arousal, awakening or ≥ 3% desaturation	**HYPOPNEA A** • Drop in nasal air pressure transducer amplitude by ≥ 30% baseline • Duration ≥ 10 sec • Associated with ≥ 4% desaturation • ≥ 90% of duration meets amplitude criteria **HYPOPNEA B** • Drop in nasal air pressure transducer amplitude by ≥ 50% baseline • Duration ≥ 10 sec • Associated with ≥ 3% desaturation or arousal • ≥ 90% of duration meets amplitude criteria
RERA	• Duration ≥ 2 missed breaths • Flattening of nasal air pressure transducer waveform • Increased work of breathing • Sequence leads to arousal • Drop in amplitude < 50%	• Duration ≥ 10 sec • Flattening of nasal air pressure transducer waveform or increased respiratory effort in sequence of breaths leading to arousal • Does not meet criteria for apnea or hypopnea

Source: Accardo JA, Shults J, Leonard MB, Traylor J, Marcus CL. Differences in overnight polysomnography scores using the adult and pediatric criteria for respiratory events in adolescents. Sleep. 2010;33(10):1333-9.

Chapter 2

Relationship between Sleep Quality and Accomplishment of Daily Life Habits in Children with Down Syndrome

Relationship between sleep quality and accomplishment of daily life habits in children with Down syndrome

Abstract

Objectives: The goal of this study was to describe sleep patterns and accomplishment of daily life habits in children with Down syndrome and to investigate the relationship between subjective indicators of sleep disturbance with accomplishment of various daily life habits domains.

Design: Cross-sectional study with an Internet sample

Setting: Online survey filled out at home

Participants: 110 parents of children with Down syndrome (DS) and 29 parents of children with typical development (TD), age 5 to 18 years.

Interventions: N/A.

Measurements and Results: Children's Sleep Habits Questionnaire was used to collect information about sleep disturbances in 8 domains (subscales) and a total score. The Life Habits (Life-H) questionnaire was used to collect information about daily life habits in 11 domains. Multivariable regression modeling was used to assess the associations between sleep quality (disturbances) and the accomplishment of daily life habits. Sleep disordered breathing was a significant explanatory factor in 10 out of 11 daily life habits and the total Life-H score. Sleep anxiety and parasomnias influenced the accomplishment of life habits in children with DS more significantly than children with typical development. When evaluated in multivariable models in conjunction with the other 7 domains of sleep disturbances, SDB was the most dominant explanatory factor for accomplishment of life habits.

Conclusions: Sleep disturbances are negatively related to accomplishment of daily life habits. Prevention and treatment of sleep problems, in particular sleep disordered breathing, in children with DS may lead to enhanced accomplishment of daily life habits and activities.

Key words: Down syndrome, sleep disturbance, accomplishment, life habits

Introduction

Children with Down syndrome (DS) are at greater risk for obstructive sleep apnea (OSA) and other sleep disturbances than children with typical development (TD). In the past fifty years a variety of clinical and parent report studies have documented sleep problems in children with DS (1). Clinical and polysomonographic studies have described the architectural and clinical characteristics of sleep in children with DS: lower rapid eye movement (REM) duration and preponderance of stage one and two sleep (2, 3); episodic oxygen desaturation and increased inspiratory resistance and stridor (4, 5); increased awakenings, arousals, and body movements (2, 6, 7); and, reduced high-frequency and increased low-frequency heart rate (8). Southall and colleagues first reported the widespread prevalence of OSA in children with DS in 1987 (4); since then, several studies have estimated the prevalence of OSA in the pediatric DS population, ranging from 54% to over 90% in clinical populations (9-12) and, from to 24% to 31% in non-clinical, community-living populations (5, 13).

Parents' perceptions and observations of children's sleep in the home environment have been described in previous research. Carter et al. (14) reported rampant problems such as restlessness during sleep (58%), night-wakings (40%) and daytime tiredness (70%). A recent study (Breslin 2011) reported loud snoring, cessation of breathing, or snorting and gasping during the night—all symptoms of sleep disordered breathing (SDB)—in 60% of the study sample. Yet another parent report study by Rosen et al. (15) underscored the need for continued SBD monitoring even after surgical intervention, given 47% of parents reporting witnessed apneas following adenotonsillectomy in their child with DS.

While the presence of sleep problems has been reported extensively in clinical and community studies, none have examined the health and functional implication of sleep disturbances in this population of children. No studies have systematically investigated the relationship of sleep with the accomplishment of usual day-to-day life habits in children with Down syndrome. The objective of this study was to measure and describe both sleep characteristics and daily life habits in a group of children with DS using well-established questionnaire tools; and to examine the relationship of these two domains: sleep disturbances and accomplishment of daily life habits. This is an important area to address within DS, as it is known that sleep difficulties in the general population of children are linked to decreased effective function in daily activities as well as impairments in mood, behavior and daily performance (16, 17). It is also well know that children with DS function less effectively in their day-to-day life than children with TD. To a large extent this difference in function is generally attributed to developmental delay caused by the genetic condition that defines Down syndrome. However, if part of this deficiency can be mitigated by improved sleep in children with DS it is critical to uncover the potential relationship between sleep and day-time function within this population as it may lead to enhanced accomplishment of day-to-day activities of life and improved quality of life for children and their families. Also, since adequate sleep is associated with better cognitive performance and learning, improvements in these domains might further support the child’s active participation in developmentally appropriate accomplishment of day-to-day life habits (16).

A conceptual model adapted from the Lee et al. model of sleep and health consequences of sleep loss, forms the theoretical framework for this study (18). The model posits that lack of adequate sleep, due to sleep deprivation and sleep disruption, leads to adverse health outcomes and daytime consequences such as impaired function, fatigue, impaired short-term memory and problem solving, and, impaired social and family interactions. A child with disrupted low-quality sleep may be excessively tired during the day, leading to poor accomplishment of daily life habit, and lower participation level in typical daily activities, further leading to poorer quality of life. Specifically, this study examines the relationship between sleep indicators and the accomplishment of day-to-life habits. It is hypothesized that while children with DS generally have lower levels of accomplishment of daily life tasks and habits than their typically-developing peers, those who have poor quality sleep fair even worse on the accomplishment of life's daily habits and activities.

Key Questions:

1) What are the descriptive characteristics of sleep in children with DS and how do they compare with a sample of children with TD?
2) What are the levels of accomplishment of daily life habits and activities of children with DS and how do they compare with children with TD?
3) What is the relationship between sleep characteristics and accomplishment of day-to-day life habits in children with DS?

Methods

This Internet survey study was approved by the Institutional Review Board at the University of Washington. All participants received a consent form by e-mail and provided electronic consent prior to completing the survey. The study was a cross-sectional survey of parents of children with and without DS, ages 5 to 18 years.

Participant Recruitment and Data Collection

The survey announcement was posted three times, between June and September 2012, on an English language international listserv for a Down syndrome support group with a membership of approximately 700 members during the period of announcement postings. The majority of listserv members were from the United States (U.S.) (88%) and other English speaking countries, Canada, United Kingdom, Australia and New Zealand (7%), with the remaining 5% from countries in Europe, Asia, Middle East and South America. The announcement was also posted on the U.S. National Down Syndrome Society's "Directory of Current Studies," and the greater Seattle area Down Syndrome listserv and newsletter. Recipients of the announcement were encouraged to forward the announcement to other families in their circles. Parents of children with DS were asked to forward the announcement to their friends and family who had children with TD. Parents interested in participating contacted the investigator by phone or e-mail. Each parent could participate only one time, reporting on only one of their children. Siblings were not allowed to be reported on by the other parent. An incentive was offered for participation in the survey, a drawing for seventy-five $25 gift cards at the end of participant recruitment period. Recruitment was carried out from June to November of 2012. Parents reported the DS or TD status of their child, and the birth month and year of the child, the only qualifying requirements for participating in the study in addition to English language ability. No recruitment quota was established, but the expected number of participants was at least 100 parents, with a DS:TD ratio of 3:1.

Once a parent agreed to participate in the 45 minute Internet survey, they received a private non-transferable survey link by e-mail. Data were collected anonymously on the survey with no identifying information within the survey. E-mail addresses were deleted once data collection concluded and incentives were sent to participants. Research Electronic Data Capture (REDCap), a secure web-based application for electronic data collection and management hosted at the University of Washington, was used for developing the Internet data collection tool and database (19).

Parents were expected to complete the survey in one session, but were informed that once started the survey could be completed later if necessary, via a private reentry code given to the participant when exiting an unfinished survey. Among the 155 enrollees who received a private survey link, 139 (90%) participated. Figure 2.1 is a flow chart of participants, broken down by DS/TD status. Enrollees who had not opened the survey or had left it unfinished received up to three reminders before the survey closing date, unless they had requested to withdraw from the study. Among 16 enrollees who never opened the survey two contacted the investigator and requested to withdraw due to lack of time. Nineteen participants had partial surveys; six contacted the investigator with reasons for incompletion, lack of time (n=3), computer problems (n=2) and dislike for survey questions (n=1). Parents who contacted the investigator about computer problems were offered a hard copy of the survey with postage paid return envelopes; one parent accepted and returned the completed.

Measures

Demographic and health characteristics

Parents completed questions about place of residence, relation to child, gender, age, height and weight of child, presence of siblings, frequency of exposure to tobacco smoke, and if the child had ever had any of the following: sleep study, diagnosis of sleep apnea, tonsillectomy, use of continuous positive airway pressure (CPAP) device, heart surgery, or diagnosis of gastrointestinal disease. Parent-reported height and weight were used to calculate body mass index (BMI) percentile using the Centers for Disease Control and Prevention's (CDC) Children's BMI Tool for Schools (20). The same BMI standard was used for children with and without DS.

Sleep characteristics

Sleep characteristics of children were determined using the well-established Children's Sleep Habits Questionnaire (CSHQ) (21), which has been used in numerous studies of children's sleep, including studies of children with DS. (14, 22) The CSHQ is a 45-item questionnaire of which 33 items are grouped into 8 conceptual domains (subscales). The domains are: bedtime resistance, sleep onset delay, sleep duration, sleep anxiety, night wakings, parasomnias, SDB, and daytime sleepiness. The questions ask about the frequency of a particular sleep habit during a typical week. Each item in the subscales, for example "needs parent in the room to sleep", is rated from 1 to 3 respectively as "usually, 5-7 times a week," "sometimes, 2-4 times a week," or "rarely, 0-1time a week." Item scores are reversed if necessary, depending on the wording of the question, such that a higher score reflects more sleep disturbance. Subscales can range from 1 to 3 for a one-item domain (sleep onset delay), to 8-24 for an eight-item domain (daytime sleepiness). A total "sleep disturbance" score is calculated by the addition of all subscales (total CSHQ). Internal consistency (community sample Cronbach's alpha [CA] 0.68; clinical sample CA 0.78), and test-retest reliability (Spearman's rho range of 0.62-0.79), have been deemed acceptable for the CSHQ which has been normed in typically-developing healthy children and in clinical populations (21). The CSHQ includes weekday and weekend bed-time, wake-time, and duration of sleep. Table 2.1 shows the detail of questions comprising the subscales of the

CSHQ. The subscales of CSHQ within the present study were compared with previously published results in children with DS and TD to check for general consistency.

Accomplishment of daily life habits

Day-to-day accomplishment of life habits was assessed using the Life Habit Questionnaire (Life-H) which is specifically designed for children with disabilities (23). The short version of this questionnaire consisting of 63 items was included in the Internet parent survey of the present study. These items form twelve domains of life habits: nutrition, fitness, personal care, communication, housing, mobility, responsibilities, interpersonal relationships, community life, education, employment, and recreation. The original domain names above are used by the authors of Life-H (23). Fauconnier and colleagues renamed several domains, making the names more closely reflective of their respective content. This manuscript uses three of Fauconnier et al.'s domain names (24). The renamed domains are: "nutrition" to "mealtimes," "housing" to "home life," and, "education" to "school." The employment domain, consisting of one item, was not used in the present analysis as this domain was not applicable to most children in the study. For each item a score of 0 to 10 is possible. The item score is a composite of two aspects, 1) level of difficulty for the child: "no difficulty," "with difficulty," "accomplished by a proxy" and "not accomplished"; and 2) type of assistance needed to accomplish the task: "no assistance," "assistive device," "adaptation," and "additional human assistance," indicating human assistance in addition to what a typical child of the same age usually requires. The subscales and total scores are normed and weighted and standardized, as per directions for the instrument, such that each subscale ranges from 0 to 10. A higher score indicates better accomplishment of daily life habits and activities. The psychometric qualities of

Life-H have been assessed, with high intrarater reliability and intraclass correlation coefficient values of 0.78 or higher for 10 subscales; and are acceptable for use in assessing children with disabilities by parent report (23). The Life-H has been used in a number of studies assessing the accomplishment of daily life habits and participation in life activities of children with disabilities (25, 26), but it has not been used previously for assessing accomplishment of daily life habits and activities of children with DS. Table 2.2 shows the details of items composing the subscales of the Life-H questionnaire.

Statistical Analysis

Stata software version 12.1 (27) was used for statistical analysis. Statistical tests were two-sided with significance level set at probability (p) <0.05. Descriptive demographic and health characteristics of the sample were summarized by listing means and standard deviation for continuous variables and frequencies for categorical variables. These characteristics were compared between groups with and without DS by t-tests for continuous variables, and chi-square tests for categorical variables. Sleep characteristics derived from the CSHQ and daily life habits and activities derived from the Life-H questionnaire were summarized and compared between the two groups. Additionally, comparison was made by dividing all children into two age-groups: 5 to 12 years, and 13 to 18 years. This age grouping was based on previous studies of children with DS and children with TD using the CSHQ (14, 21), and reflects the notion that younger children's sleep is developmentally different than teenagers' sleep.

Regression analyses were performed to assess the relationship between sleep variables, explanatory variables, and accomplishment daily life habits and activities, the outcome variables. The goal of this assessment was to describe the trends and to test the hypothesis that sleep disturbances negatively affect the accomplishment of daily life habits. Each sleep domain variable was used independently in the models in order to assess the relationship sleep disturbance scores without redundancy in the models. Three sets of ordinary least squares (OLS) regression models were run. First, models including all children with and without DS to determine the association of sleep with daily life function on all children, while controlling for DS status, age, and gender; these results were presented in a regression table. Secondly, OLS regression models were run within the DS group controlling for age and gender; and third, regression models within children with TD, controlling for age and gender. The secondary sets of models, within DS and within TD, were run in order to check for any interactions within these groups by age, or gender. All models were tested for interaction between DS status and age, DS status and gender, and, DS status and the independent sleep indicator variable in the model (bedtime resistance, sleep onset delay, sleep duration, sleep anxiety, night wakings, parasomnias, SDB, and daytime sleepiness, or total CSHQ score); and any interaction between age and gender. F tests were used to determine if the R^2 values attained with and without interaction terms in the models were significantly different.

Finally, OLS regression models were run with all sleep disturbance variables, DS status, age, and gender, for all Life-H outcome variables. The purpose of this analysis was to evaluate the role of SDB in conjunction with other sleep disturbance variable. These results were summarized in a table.

Age was a continuous variable in all regression models. DS and gender were categorical variables. All outcome variables, Life-H scores, and explanatory variables, CSHQ scores, were continuous. R-squared (R^2) for models was noted as an indicator of the fit of the model.

Coefficients of regression and p-values were reported in a regression summary table. Any interactions were noted within results.

Results

Demographic, Health and family characteristics

Participants were all parents who responded to questions about their child who lived with them at the time of the survey. A majority of respondents were from the United States, and were mothers. Table 2.3 summarizes the characteristics of the children. The samples of children with and without DS were balanced with respect to presence of younger and older siblings and exposure to cigarette smoke. A majority of children with DS were male and the majority of the TD sample was female. The gender imbalance and variation in age were taken into account in the statistical analyses. As expected, children with DS were more likely to be overweight, to have ever had a sleep study, ever been diagnosed with sleep apnea (35%) or gastrointestinal illness; and were more likely to have ever had tonsillectomy or heart surgery. Among children with DS 15% had used a continuous positive air pressure device at some point, where none of the children with TD had ever used such device. Also, none of the children with typical development had ever had a sleep study, been diagnosed with sleep apnea or had heart surgery.

Sleep Patterns

Table 2.4 summarizes parent-reported bed time, wake time and hours of sleep for weekdays and weekends by DS status. On average, children with DS had earlier wake and bed times during the week and weekends, leading to statistically significant greater hours of sleep during weeknights, largely due to significantly earlier bed times. There was no statistically significant difference in the amount of sleep time during weekends. The sleep disturbance variables derived from the CSHQ were summarized by DS status and age group in Table 2.5. Children with DS were reported to have significantly more night wakings, parasomnias and symptoms of SDB. There were age variations in some of the indicators of sleep disturbance, but overall children with and without DS were reported to have similar bedtime resistance, sleep onset delay (falling asleep within 20 minutes) and sleep anxiety.

Figure 2.2 shows a comparison between the CSHQ subscale scores attained by the present study and two previous studies that used CSHQ, for younger children. Owens et al. had a sample of 370+ children with TD, age 4-10 years (21); and Carter et al. had a sample of 24 children with DS, 4-12 years (14). The Carter study and the present study both had higher sleep disturbance scores; the Carter study had higher scores in five of eight domains than the present study. The sample size for the present study is larger than Carter's study, and is comprised of a more diverse group of children with DS from around the United States and other countries. The Carter study sample was from the city of Southampton in England.

Description Daily Life Habit Domains

Daily life habits, as characterized by the Life-H questionnaire, were compared between children with and without DS and by age group. As this questionnaire is primarily designed and normed for children with disabilities, all subscales and total score were significantly different between children with and without DS. As expected, the scores for children with DS were generally normally distributed with a wider range and larger standard deviations, compared to the tighter range and smaller standard deviations, and skewed distribution of scores towards the higher end, for children with TD. Table 2.6 contains a summary of all Life-H scores and standard deviations.

The association between sleep disturbance and accomplishment of daily life habits

Regression analyses assess the association of sleep indicators with accomplishment of daily life habits and activities, and to test the hypothesis that sleep disturbances can be an explanatory factor for accomplishment of daily life habits. Eleven subscales (mealtimes, fitness, personal care, communication, home life, mobility, responsibilities, relationships, community life, school, recreation) and the total scores of Life-H were outcome variables for regression models. Explanatory variables were CSHQ indicators of sleep disturbance: bedtime resistance, sleep onset delay, sleep duration, sleep anxiety, night wakings, parasomnias, SDB, daytime sleepiness, and the total score of the CSHQ questionnaire; each along with DS status, age and gender. As expected DS status was a highly significant explanatory factor in all domains of Life-H. Table 2.7 summarizes the results of these analyses. Below the detail of results are presented with respect for each sleep disturbance subscale.

Bedtime resistance. Bedtime resistance refers to a child's delaying or refusing to go to bed through various behaviors, resulting in a potentially shorter duration of sleep. Bedtime resistance was significantly associated with lower accomplishment scores in mealtimes, fitness, personal care, relationships, community life, school and total Life-H score. There were no statistically significant differences between children with and without DS with respect to this explanatory factor for life habit outcomes. The Life-H domain most associated with this score was community life; for every point increase in the bedtime resistance score there was a 0.52 point decrease in community life score.

Sleep onset delay. Sleep onset delay was defined as not falling asleep within 20 minutes of going to bed. This subscale was not significantly associated with any of the Life-H accomplishment scores in this study. Within this study there were no differences in sleep onset delay by age, gender or DS status.

Sleep duration. Sleep duration is a measure of parents' perception of the adequacy of the length of sleep a child gets at night and if that amount of sleep is consistent from night to night. Sleep duration was significantly associated with accomplishment of mealtime habits, personal care, responsibilities, and community life for all children with and without DS. Sleep duration was most significantly and negatively associated with community life in children with DS, for every point increase in sleep duration subscale (higher score is worse) there was a 0.35 point decrease in community life score.

Sleep anxiety. Sleep anxiety is a measure of negative and fearful feelings at sleep time, at home or away from home, potentially leading to a lack of adequate sleep. Sleep anxiety was significantly related to fitness, personal care, relationships, community life, school and the total Life-H score. Sleep anxiety was one of two explanatory sleep disturbance variables (the other was parasomnias) where there was a statistically significant difference between children with and without DS with respect to the influence of the measure on one or more of the Life-H accomplishment outcomes. For example, every point increase in the sleep anxiety score was associated with a 0.43 point decrease in the fitness score among children with DS. The corresponding regression coefficient for children with TD was -0.04, meaning that while for all children there was a statistically significant decrease in fitness score, the slope of the regression line was significantly steeper for children with DS. This was determined by the significance of the interaction term for DS and sleep anxiety (DS [0 or 1] x sleep anxiety score) within the multivariable model (F test p-value < 0.05) . The addition of the interaction term significantly increased the fit of the model (from $R^2 = 0.28$ to $R^2 = 0.31$).

Night Wakings. This subscale is a measure of the frequency of a child's wakings through the night and if the child moves to a sibling's or a parent's bed, disturbing the child's sleep (not to mention the sibling's or the parent's). Night wakings was significantly and negatively associated with fitness, responsibilities, community life and school. For example, children with DS had a 0.48 point decrease (0.44 for all children) in responsibilities score for every point increase in night wakings score.

Parasomnias. Parasomnias score consists of a measure of various unconscious, and generally undesireable, behaviors or emotions during sleep such as sleep talking, bedwetting, grinding teeth (28) which compromise the quality of one's sleep. Parents of children with DS reported more parasomnias than children with TD's parents. Parasomnias were associated in lower accomplishment scores in mealtimes, fitness, personal care, relationships, school, and the total Life-H score. In children with DS every point increase in parasomnias score was associated with a 0.43 point decrease in the fitness score, where for children with TD the slope was in the opposite direction with a non-significant slope of +0.04. The interaction term for DS and parasomnias (DS [0 or 1] x parasomnias score) was significant in the multivariable model indicating a significant difference between the coefficients of regression for children with and without DS. The addition of the interaction term significantly increased the R^2 from 0.31 to 0.33 (F test p-value < 0.05). When measured in all children, without considering the interaction described, the coefficient of regression was a statistically significant 0.35 point decrease in the Life-H fitness score for every point increase in the CSHQ parasomnias score.

Sleep disordered breathing. SDB scores measure the symptoms of SDB: snoring, temporary cessation of breathing, snorting and gasping. SDB is the general term for conditions like obstructive sleep apnea that involve abnormal breathing patterns during sleep. The SDB score was a significant explanatory factor for 10 out of 11 Life-H accomplishment scores in children with DS: fitness, personal care, home life, mobility, responsibilities, school and recreation, in addition to being an explanatory factor for the total Life-H score. Most significantly SDB was associated with scores for accomplishment in home life and responsibilities, where for every point increase in the SDB score there was a decrease of a 0.42 to 0.44 point on the Life-H accomplishment score for children with DS and 0.40 for all children.

Daytime sleepiness. This variable is the parent's perception of how tired a child seems during the day. Daytime sleepiness was significantly associated with a single Life-H subscale in this study: accomplishment in school in all children—perspicacious in this context. Children with DS had a 0.19 point decrease (0.17 for all children) in the Life-H school score for every point increase in the daytime sleepiness score.

Total CSHQ sleep disturbance score. This total score was significantly associated with accomplishment in mealtimes, fitness, personal care, responsibilities, relationships, community life, school and the total Life-H score. The effect sizes ranged from a 0.06 to 0.12 point decrease in the accomplishment score for every point increase the total CSHQ score, a smaller point decrease than individual categories of sleep variables such as SDB and sleep anxiety, but the total CSHQ score has a large range, 33-99 points.

These results are consistent with the study hypothesis that sleep disturbances negatively affect the accomplishment of daily life activities over and above the deficiency that is associated with DS status alone.

The role of SDB score among other sleep disturbance variables

Table 2.8 shows the results of a series of multivariable regression models, where the significance of the SDB score was tested against other sleep disturbance variables with all of the Life-H outcomes. The models were controlled for DS status, age and gender. The SDB score demonstrates a consistent pattern of negative association with all Life-H outcomes, with the exception of the communication score in Life-H.

Discussion

All the multivariable models in study regression tables (Table 2.7 and 2.8) were adjusted for DS status, age and gender. In all models DS status was a strong statistically significant factor in the Life-H scores. It is well known, as demonstrated in these models, that children with Down syndrome generally accomplish life habits and activities on a lower level than children with TD. However, the presence of Down syndrome, while a very important explanatory factor, may not be the only factor that determines functional and accomplishment outcomes in children with DS, according to these results. Other explanatory factors that may well influence these outcomes include family setting, family behaviors, intensity of educational interventions and their availability, general health and environment, and sleep, to name a few. This study provides support for the hypothesis that sleep disturbances are important explanatory factors influencing several functional outcomes in children with Down syndrome. The magnitude of this influence is significant, translating into over 20% improvement in scores of several life habits investigated in this study.

Sleep duration score was significantly higher for older (13-18 years) children with TD, indicating shorter sleep time in this group and longer sleep duration in the DS group; but daytime sleepiness score was significantly greater in children with DS in the same age range, potentially indicating more fragmented sleep due to SDB. Sleep disordered breathing was a significant explanatory factor in all domains of life habits in children with DS, with the exception of communication. The significance of SDB in the models presented in Table 2.8 is consistent with

SDB's association with other sleep problems (29, 30), such as night wakings, length of sleep duration, parasomnias, and even sleep anxiety and bedtime resistance; where breathing difficulty could be thought of as an instigator for these additional disturbances, some of which are behavioral rather than physiological like SDB. The statistical significance of these models and the efficiency of the models is not a matter of importance in this analysis; rather the consistent pattern of SDB is of importance. The number of explanatory factors in these models is 11, which makes the standard errors for explanatory variables large and thus makes it more difficult and more conservative to achieve statistical significance. This analysis shows that the presence of SDB in the models, where other sleep variables are included, generally overpowers the other sleep factors.

This analysis was exploratory for the purpose of finding avenues to intervene with to improve outcomes in children. The exploratory nature of this analysis is the reason for looking at over 100 models, considering all sleep disturbance subscales and Life-H outcomes. Total scores alone could have been tested in Life-H and CSHQ (and they would be statistically significant); but these total score would have only shown general trends without specifically pinpointing problem areas. This exploratory analysis indeed showed the importance of SDB in accomplishment of life habits in children with DS, showing a consistent pattern, even if not always statistically significant. SDB has been known as a major problem in Down syndrome since the 1980s; this analysis shows that SDB could actually be implicated in accomplishment of daily life habits and activities in children with DS, over and above the contribution of the genetic condition itself.

None of the sleep disturbance indicators or the total CSHQ score was an explanatory factor in communication skills of children with DS. Communication difficulties in children with

DS are generally extensive, complex and related to oral motor and hearing skills (31). Based on the present results it appears that the etiology of communication difficulties in DS is not related to sleep as some of the other daily life habits appear to be.

The imbalance in sample limits interpretations about the TD group; nevertheless, this is the only study of its type that has related CSHQ to Life-H in children with typical development. The trends for the relationship of sleep disturbances with accomplishment of life habits are the same as children with DS, but statistical significance could not be achieved for most observations within the TD group because of the small sample size of TD and the small effect sizes in the TD group. A larger sample size similar to the DS sample might have likely produced significance levels for children with TD as it did for the children with DS.

A few other limitations of this study need to be considered. The questionnaires were originally developed for younger ages of children, CSHQ for children 4 to12 years, and Life-H for children 5 to 13 years. The present study included children up to 18 years old. These questionnaires have however both been used previously in older populations of children with disabilities (14, 32). Of note, one domain in the Life-H questionnaire, the “fitness” domain, include questions about sleep. There is need for refinement of this Life-H domain for use within studies that investigate sleep.

No income or race information was collected within this study; socioeconomic variations likely exist within this cohort, but it was not goal of this study to investigate the effects of these potentially confounding factors or other known and unknown factors that can influence accomplishment of daily life habits and activities. The sample was likely diverse, as the participants were from many different regions across the world. Some participants, unsolicited, indicated their race or ethnicity during initial communication with the investigator—this information was not recorded or used in any way for analysis or description.

The methodology in this study was subjective, relying on parent report; however, well-established and previously-tested questionnaire tools were used to conduct the study. As with other parent report studies of sleep in children, if parents do not necessarily sleep in the same room as their child, or are deep sleepers, the parents may not know about gasps, snoring, or other SDB symptoms and parasomnias in their child. The presence of DS and other health characteristics were reported by parents. Comorbidities were not excluded from the study as most children with DS and other special needs have one or more comorbid conditions present, and some that the parent may not even be aware of (33). One parent of a child with DS reported that their child had been diagnosed with autism. The scores from that child were examined and they did not appear to be outliers and were in the same range as other children with DS.

In this analysis multiple models were tested, with 9 sleep disturbance explanatory variables and 12 Life-H outcome variables, including total scores. A Bonferroni-style correction for the p-values was not adopted (34). This was an exploratory subjective study with good theoretical backing. The concordance of these models is confirmatory of the patterns observed. No causal inferences were made. The trends observed in these data need to be studied further with objective methodology, such as actigraphy, for measuring sleep.

Conclusions

Contrary to many studies of sleep in children with DS, the Internet sample for this study did not represent a clinical population, but included parents from 21 US states and six other countries. The results may be generalizable to the community living children with DS. Many clinical studies (4, 10), and even parent report studies (14), have reported rampant sleep problems with high prevalences (14). Over the past 20 years awareness of sleep problems in children with DS has increased. Therefore it is not surprising that in this study 48% of parents reported overnight sleep studies, 34% reported sleep apnea diagnosis, 55% reported tonsillectomy, and 15% reported that at some point their child had used a CPAP device. However, clinical monitoring of children with DS, even after treatment, would appear warranted, as SDB symptoms often persist even in children who had tonsillectomies, an observation in the present study which is similar to previous studies of sleep in DS (35).

To date this investigation has the largest sample for a parent-report study of sleep in children with DS. The CSHQ questionnaire was used in previous studies and the present descriptive results for sleep scores are generally in agreement with past studies (14, 22). The present DS sample was compared with a small sample of children with TD. For certain sleep indicators and age groups the CSHQ scores for children with TD were similar to those of children with DS. This is a departure from previous studies with TD comparison groups which tended toward highly significant differences between TD and DS/clinical group (14, 21), potentially indicating increased sleep problems in TD populations as indicated by recent studies (36); or it is possible that parents of children with TD *and* sleep problems may have self-referred to this study more often than parents who did not have a child with sleep problems.

What this study adds: For the first time this study has demonstrated that there is an association between sleep disturbances and accomplishment of daily life habits among children with DS. Treating sleep problems in DS may lead to improved accomplishment of daily life habits and activities. There is a need for future objective studies to further understand the relationships between sleep and functional abilities of children with DS.

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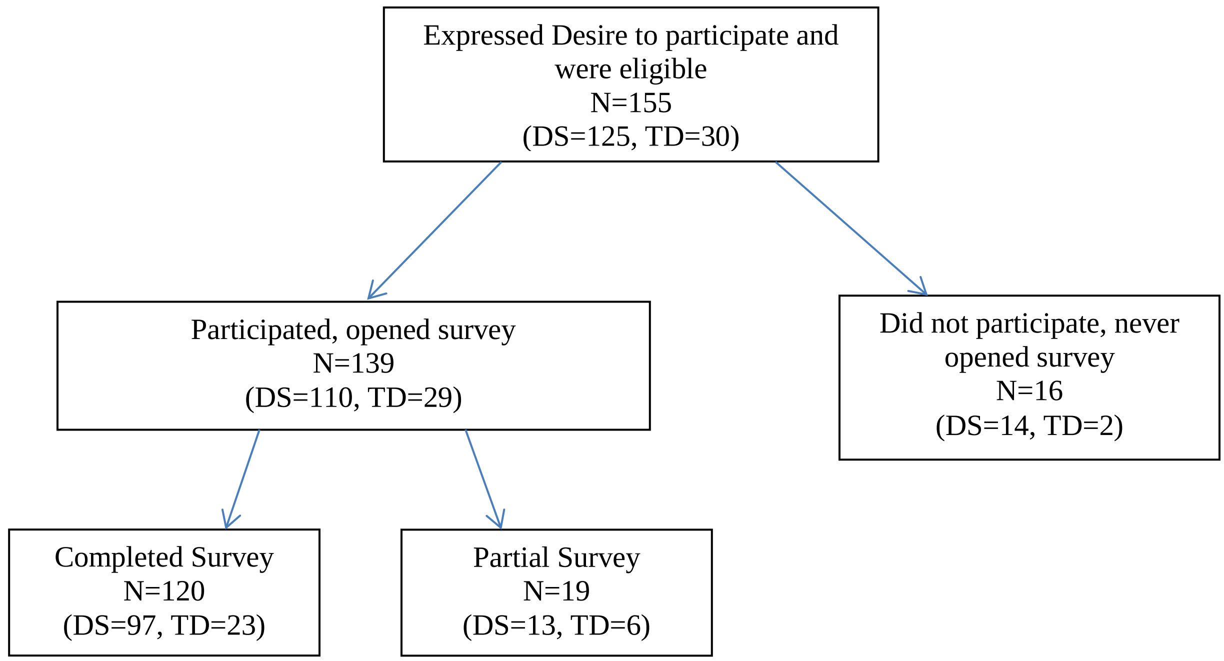
Figure 2.1. Flow Chart of Survey Participants



DS = Parent of a child with Down syndrome
TD = Parent of a child with typical development

Figure 2.2. CSHQ Sleep Domain Scores by Study

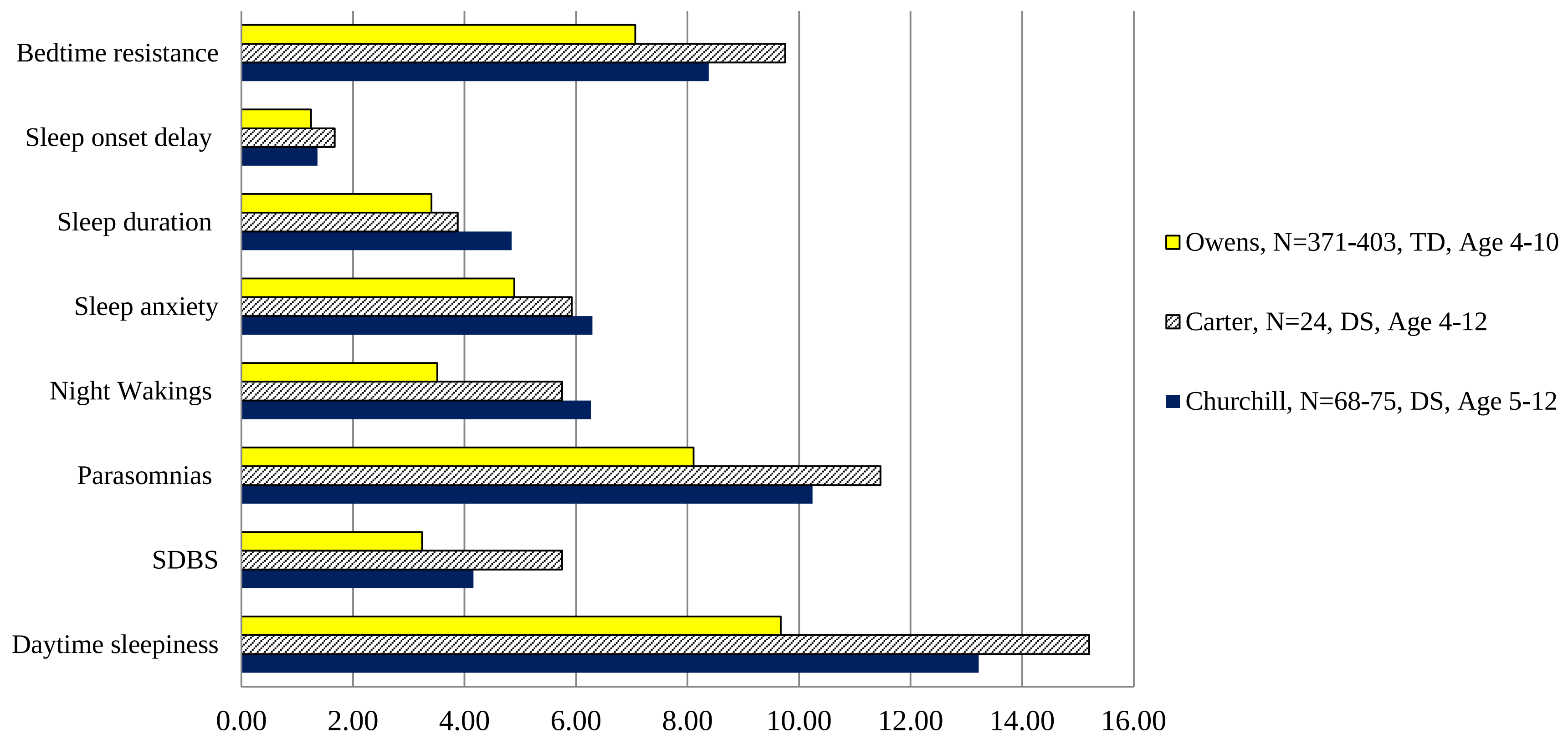


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Table 2.1. Items for subscales of Children's Sleep Habits Questionnaire

1. Bedtime Resistance
- Goes to bed at same time
- Falls asleep in own bed
- Falls asleep in other's bed
- Needs parent in room to sleep
- Struggles at bedtime
- Afraid of sleeping alone

2. Sleep Onset Delay
- Falls asleep in 20 minutes

3. Sleep Duration
- Sleeps too little
- Sleeps the right amount
- Sleeps same amount each day

4. Sleep Anxiety
- Needs parent in room to sleep
- Afraid of sleeping in the dark
- Afraid of sleeping alone
- Trouble sleeping away

5. Night Wakings
- Moves to other's bed in night
- Awakes once during night
- Awakes more than once

6. Parasomnias
- Wets the bed at night
- Talks during sleep
- Restless and moves a lot
- Sleepwalks
- Grinds teeth during sleep
- Awakens screaming, sweating
- Alarmed by scary dream

7. Sleep Disordered Breathing
- Snores loudly
- Stops breathing
- Snorts and gasps

8. Daytime Sleepiness
- Wakes by himself
- Wakes up in negative mood
- Others wake child
- Hard time getting out of bed
- Takes long time to be alert
- Seems tired
- [Falls asleep] Watching TV
- [Falls asleep] Riding in car

Table 2.2. Life Habits Questionnaire Domains and Items

1. Mealtimes
Selecting appropriate food for snacks and meals, according to taste and particular needs (quantity, type of food, etc.)
Taking part in meal preparation (including using certain kitchen appliances)
Eating meals (including using dishes and utensils, standard table manners, etc.)
Eating out at a restaurant (table service and fast food)

2. Fitness
Getting in and out of bed
Sleeping (comfort, duration, soundness)
Engaging in physical activities to maintain or improve physical health or fitness
Engaging in quiet activities that are relaxing or require attention (listening to music or a story, memory games, etc.)

3. Personal Care
Attending to personal hygiene (washing, toothbrushing, hair combing, taking a bath or shower, etc.)
Using the toilet at home (including flushing method or device)
Using the toilet elsewhere than at home (including flushing method or device)
Dressing and undressing the upper half of the body (including fastening buttons and zippers and choosing clothes)
Dressing and undressing the lower half of body (including fastening buttons, zippers and laces and choosing clothes)
Putting on, removing and maintaining assistive devices (orthotics, hearing aid, contact lenses, glasses, etc.)
Taking part in personal health care (first aid, following treatment instructions, medications, etc.)
Using services provided by a medical clinic, hospital, rehabilitation center, or community clinic

4. Communication
Communicating with an adult at home or in the community (expressing needs, having a conversation, etc.)
Communicating with a young person at home or in the community (expressing needs, having a conversation, etc.)
Communicating with a group of people at home or in the community (expressing ideas, having a conversation, etc.
Communicating in writing (writing words, sentences, a short text, etc.)
Reading and understanding written information (words, books, pictographs, written instructions, signs, etc.)
Using a telephone at home
Using a computer
Using a television, a video recorder, a sound system, an iPod, etc

5. Home life
Taking part in housekeeping tasks (light cleaning, making bed, tidying up)
Taking part in maintaining the grounds (lawn care, snow removal, etc.)
Entering and exiting the home
Moving around within the home
Using the furniture and equipment at home (table, storage space, lighting, outdoor play equipment, etc.)
Moving around outside the home (backyard, grounds)

Table 2.2. Life Habits Questionnaire Domains and Items (continued)

6. Mobility
Moving around streets and sidewalks (including crossing streets)
Moving around on slippery or uneven surfaces (snow, ice, grass, gravel, etc.)
Riding a bicycle (as means of transportation, for leisure, etc.)
Being a passenger in a vehicle (car, bus, taxi, etc.)

7. Responsibilities
Recognizing the value of coins and bills and using them correctly
Managing pocket money (savings, small purchases)
Using a bank card and an automated teller machine (ATM)
Shopping, running errands (choosing and paying for merchandise)
Respecting other people's property and rights (personal effects, rules of conduct)
Taking charge of himself / herself, standing up for own rights
Helping out at home (doing a service for parent or other family members)

8. Relationships
Maintaining a loving relationship with parents
Maintaining a loving relationship with other members of immediate family (brothers, sisters, etc.)
Maintaining a loving relationship with other relatives (grand parents, cousins, etc.)
Maintaining friendly or other social ties with other young people (school, recreational activities, etc.)
Maintaining social ties with adults (teachers, instructors, etc.)

9. Community Life
Participating in the activities of community groups, student association, etc. (e.g. scouts, class committees)
Participating in religious or spiritual activities

10. School
Getting to school, entering, moving around in the school (including carrying a school bag)
Taking part in learning activities at school (workshops, classes, assignments)
Taking specialized classes (PE, music, etc.)
Using school facilities (e.g. cafeteria, school yard, gym, etc.)
Doing homework
Taking part in school activities (extra-curricular activities, outings, field day, etc.)

11. RECREATION
Taking part in sports or recreational activities (sports and games, outdoors recreational activities)
Playing individual or group games, indoors or outdoors (card games, ball games, video games)
Attending sporting events (baseball, football, etc.)
Taking part in artistic, cultural, or craft activities (music, dance, arts and crafts, etc.)
Attending artistic or cultural events (concerts, movies, theatre, etc.)
Taking part in tourist activities (traveling, visiting natural and historic sites, etc.)
Getting to, entering and moving around in local recreational facilities (library, municipal recreation center, etc.)
Using local recreational facilities (library, municipal recreation center, etc.)

Table 2.3. Characteristics of the sample by Down syndrome status

	DS n=110 Mean (sd)	TD n=29 Mean (sd)	p-value T-test
Age in years	11.05 (4.25)	12.52 (3.90)	0.095
BMI percentile	72.54 (26.73)	59.16 (31.47)	0.023
	%	%	p-value Chi-square test
Gender, Male	75.45	20.69	<0.001
Age group			0.099
5 to 12 years	68.18	51.72	
13 to 18 years	31.82	48.28	
Relation of respondent to child			0.796
Mother	95.45	96.55	
Father	4.55	3.45	
Siblings			0.783
None	13.76	13.79	
Younger sibling(s) only	28.44	37.93	
Older sibling(s) only	35.78	31.03	
Younger and older siblings	22.02	17.24	
Country of residence			
USA	90%	100%	0.790
At risk or obese (BMI % ≥ 85)	48.18	31.03	0.098
Obese (BMI % ≥ 95)	28.18	6.9	0.017
Ever had a sleep study	48.18	0	<0.001
Ever diagnosed with Sleep apnea	34.55	0	<0.001
Ever had tonsillectomy	55.45	6.9	<0.001
Ever had heart surgery	22.73	0	0.005
Ever diagnosed with GI disease	21.82	3.45	0.022
Ever used CPAP	15.45	0	0.024
Using CPAP now	6.36	N/A	N/A
Exposure to cigarette smoke			0.205
Not at all	95.45	86.21	
Rarely: 1-2 times a month	2.73	10.34	
Occasionally: 1-2 times a week	0.91	3.45	
A few days a week: 3-4 times	0.91	0	
5-7 days a week	0	0	

DS: Down syndrome; TD: typical development; sd: standard deviation; BMI: body mass index; CPAP: continuous positive air pressure; GI: gastrointestinal

Table 2.4. Weekday and weekend bed-time, wake time, and parent-reported hours of sleep, by DS status

	DS		TD		
	Mean (sd)	Range	Mean (sd)	Range	p-value
Weekday waketime	6:32 AM (42 m)	4:36 - 8:00 AM	6:46 AM (58 m)	5:00 - 10:00 AM	0.164
Weeknight bedtime	8:34 PM (47 m)	6:30 - 10:30 PM	9:25 PM (76 m)	7:45 PM - 12:00 AM	<0.001
Weekday hours of sleep	9 h 26 m (69 m)	6 h 30 m - 12 h 0 m	8 h 49 m(95 m)	5 h 0 m - 13 h 0 m	0.026
Weekend waketime	7:11 AM (63 m)	5:00 - 10:00 AM	8:32 AM (84 m)	6:30 - 11:00 AM	<0.001
Weekend bedtime	9:10 PM (61 m)	7:00 - 12:00 AM	10:38 PM (88 m)	8:00 PM - 1:00 AM	<0.001
Weekend hours in bed	9 h 32 m (76 m)	6 h 0 m - 12 h 0 m	9 h 40 m (83 m)	6 h 0 m - 13 h 0 m	0.655

DS: Down syndrome; TD: typical development; sd: standard deviation; h: hours; m: minutes

Table 2.5. Means and standard deviations for CSHQ subscales, by DS status and age group; p-values for difference between DS & TD within age group

	Ages 5 to 12 years			Ages 13 to 18 years			All ages, 5 to 18 years		
Sub-scales of CSHQ (range)	DS n=68-75 mean (sd)	TD n=13-15 mean (sd)	p-value	DS n=32-35 mean (sd)	TD n=12-14 mean (sd)	p-value	DS n=100-110 mean (sd)	TD n=25-29 mean (sd)	p-value
Bedtime resistance (6-18)	8.38 (2.28)	7.43 (2.41)	0.160	6.50 (1.14)	6.69 (0.85)	0.586	7.80 (2.17)	7.07 (1.84)	0.116
Sleep onset delay (1-3)	1.36 (0.63)	1.47 (0.64)	0.572	1.26 (0.51)	1.36 (0.63)	0.598	1.33 (0.60)	1.41 (0.63)	0.524
Sleep duration (3-9)	4.84 (1.77)	4.00 (1.53)	0.113	4.06 (1.39)	5.17 (1.75)	0.035	4.60 (1.70)	4.56 (1.71)	0.920
Sleep anxiety (4-12)	6.29 (1.77)	6.64 (2.17)	0.521	4.97 (1.19)	4.58 (1.16)	0.337	5.86 (1.71)	5.69 (2.04)	0.667
Night Wakings (3-9)	6.27 (1.17)	5.36 (0.63)	0.006	5.79 (1.19)	5.58 (0.67)	0.578	6.12 (1.19)	5.46 (0.65)	0.008
Parasomnias (7-21)	10.24 (2.03)	8.69 (1.65)	0.012	9.64 (1.65)	8.00(2.13)	0.010	10.04 (1.93)	8.36 (1.89)	<0.001
SDB (3-9)	4.16 (1.64)	3.43 (1.16)	0.117	4.66 (1.56)	3.33 (0.89)	0.008	4.32 (1.63)	3.38 (1.02)	0.006
Daytime sleepiness (8-24)	13.00 (2.63)	13.00 (2.52)	1.00	13.22 (1.85)	11.58 (1.78)	0.012	13.07 (2.40)	12.32 (2.27)	0.160
Total CSHQ score (33-99)	52.41 (7.16)	47.64 (9.50)	0.034	49.06 (6.41)	46.17 (7.08)	0.200	51.35 (7.07)	46.96 (8.34)	0.007

DS: Down syndrome; TD: typical development; n: number; sd: standard deviation

Table 2.6. Subscales and total scores of LIFE-H questionnaire. Children with DS had scores significantly lower (p<0.01) than children with TD in all age groups and for all domains of Life Habits

	Ages 5 to 12 years		Ages 13 to 18 years		All ages, 5 to 18 years	
	DS	TD	DS	TD	DS	TD
LIFE-H Subscales	n=71/75	n=13/15	n=33/35	n=12/14	n=104/110	n=25/29
	mean (sd)	mean (sd)	mean (sd)	mean (sd)	mean (sd)	mean (sd)
Nutrition	5.72 (2.56)	9.36 (1.32)	6.36 (1.86)	9.61 (1.06)	5.93 (2.37)	9.48 (1.18)
Fitness	7.00 (2.19)	10.00 (0.00)	7.71 (1.97)	9.46 (0.94)	7.23 (2.14)	9.75 (0.68)
Personal Care	4.74 (2.33)	9.35 (0.89)	6.43 (1.77)	9.70 (0.77)	5.30 (2.30)	9.52 (0.83)
Communication	4.75 (2.11)	9.65 (0.60)	5.90 (2.41)	9.60 (0.93)	5.13 (2.27)	9.63 (0.76)
Housing	7.90 (1.78)	9.93 (0.26)	8.30 (1.13)	9.70 (0.68)	8.03 (1.60)	9.82 (0.51)
Mobility	5.49 (2.17)	9.51 (1.02)	6.45 (2.09)	10.00 (0.00)	5.81 (2.18)	9.75 (0.76)
Responsibility	3.79 (2.39)	8.93 (1.93)	4.31 (2.41)	9.42 (1.32)	3.96 (2.40)	9.17 (1.65)
Interpersonal relations	8.03 (2.30)	9.76 (0.61)	7.91 (2.17)	9.43 (1.39)	7.99 (2.24)	9.60 (1.05)
Community life	4.73 (2.82)	10.00 (0.00)	4.68 (3.07)	9.00 (1.85)	4.71 (2.89)	9.50 (1.37)
Education	5.04 (2.00)	9.91 (0.32)	6.15 (1.99)	9.19 (1.73)	5.40 (2.06)	9.58 (1.21)
Recreation	5.39 (2.42)	9.91 (0.32)	6.35 (2.13)	9.44 (1.19)	5.71 (2.36)	9.68 (0.87)
Total LIFE-H score	5.71 (1.75)	9.67 (0.45)	6.26 (1.57)	9.45 (1.05)	6.44 (1.49)	9.47 (1.02)

DS: Down syndrome; TD: typical development; n: number; sd: standard deviation

Table 2.7. Multivariable regression results: coefficients for life habit outcomes, significance and R^2

Outcomes: →	Mealtimes	Fitness	Personal Care	Communication	Home life	Mobility
Explanatory variable (score range)						
Bedtime resistance (6-18)	**-0.30*** **	**-0.38*** **	**-0.30*** **	**-0.12**	**-0.02**	**-0.09**
DS presence	-2.75***	-1.96***	-3.37***	-4.13***	-1.64***	-3.67***
Age, years	0.05	0.02	0.16***	0.08	0.02	0.08*
Gender, male	-0.60	-0.29	-0.39	-0.11	-0.11	0.01
R^2	0.37	0.32	0.53	0.45	0.18	0.40
Sleep Onset Delay (1-3)	**-0.30**	**-0.32**	**-0.22**	**-0.39**	**-0.03**	**-0.24**
DS presence	-2.94***	-2.12***	-3.67***	-4.28***	-1.73***	-3.78***
Age, years	0.09*	0.04	0.20***	0.09**	0.02	0.10**
Gender, male	-0.94**	-0.72*	-0.57	-0.19	-0.05	-0.06
R^2	0.33	0.23	0.48	0.45	0.19	0.41
Sleep duration (3-9)	**-0.27** **	**-0.15**	**-0.24** **	**-0.16**	**-0.11**	**-0.04**
DS presence	-2.71***	-1.92***	-3.45***	-4.08***	-1.60***	-3.92***
Age, years	0.09**	0.04	0.21***	0.10**	0.02	0.09*
Gender, male	-1.13**	-0.87**	-0.85**	-0.40	-0.18	-0.04
R^2	0.35	0.24	0.52	0.45	0.19	0.41
Sleep anxiety (4-12)	**-0.19***	**-0.34*** **	**-0.26** **	**-0.09**	**-0.07**	**-0.19***
DS presence	-2.88***	-2.06***	-3.48***	-4.17***	-1.64***	-3.69***
Age, years	0.05	-0.01	0.17***	0.08	0.01	0.07
Gender, male	-0.71	-0.45	-0.59	-0.13	-0.06	0.02
R^2	0.34	0.28/0.31	0.52	0.45	0.19	0.42
Night Wakings (3-9)	**-0.22**	**-0.37** **	**-0.15**	**-0.31***	**-0.08**	**-0.12**
DS presence	-2.85***	-1.89***	-3.56***	-4.08***	-1.68***	-3.67***
Age, years	0.07	0.02	0.20***	0.09*	0.02	0.08*
Gender, male	-0.85*	-0.67*	-0.57	-0.22	-0.06	-0.11
R^2	0.33	0.26	0.49	0.46	0.19	0.40
Parasomnias (7-21)	**-0.33*** **	**-0.35*** **	**-0.25*** **	**-0.03**	**-0.05**	**-0.12**
DS presence	-2.24***	-1.46***	-3.12***	-4.10***	-1.54***	-3.66***
Age, years	0.08*	0.03	0.19***	0.09*	0.02	0.09*
Gender, male	-0.85*	-0.58	-0.60	-0.20	-0.10	0.03
R^2	0.37	0.31	0.51	0.43	0.19	0.41
SDB (3-9)	**-0.29** **	**-0.29*** **	**-0.28** **	**-0.09**	**-0.40*** **	**-0.26** **
DS presence	-2.73***	-1.93***	-3.35***	-4.18***	-1.38***	-3.55***
Age, years	0.09*	0.04	0.20***	0.09*	0.04	0.09**
Gender, male	-0.71	-0.43	-0.50	-0.19	-0.09	0.14
R^2	0.35	0.27	0.51	0.46	0.34	0.42
Daytime sleepiness (8-24)	**-0.10**	**-0.11**	**-0.03**	**-0.04**	**0.00**	**-0.09**
DS presence	-2.82***	-1.99***	-3.44***	-4.04***	-1.68***	-3.57***
Age, years	0.08*	0.04	0.20***	0.10**	0.02	0.10**
Gender, male	-0.89*	-0.59	-0.74*	-0.27	-0.13	-0.03
R^2	0.33	0.23	0.48	0.44	0.19	0.39
Total CSHQ (33-99)	**-0.08*** **	**-0.07*** **	**-0.07*** **	**-0.01**	**-0.03**	**0.00**
DS presence	-2.52***	-1.76***	-3.23***	-4.14***	-1.51***	-3.75***
Age, years	0.08*	0.03	0.19***	0.09**	0.01	0.09**
Gender, male	-0.84*	-0.59	-0.67*	-0.24	-0.12	-0.12
R^2	0.37	0.28	0.52	0.45	0.21	0.40

*** $p \leq 0.01$; ** $p>0.01$ & $p \leq 0.05$; * $p>0.05$ & $p \leq 0.10$

Table 2.7. Multivariable regression results: coefficients for life habits, significance and R^2 (continued)

Outcomes: →	Responsibilities	Relationships	Community Life	School	Recreation	Total Life-H
Explanatory variable (range)						
Bedtime resistance (6-18)	**-0.12**	**-0.26****	**-0.52*****	**-0.30*****	**-0.15**	**-0.25*****
DS presence	-4.92***	-1.34**	-4.10***	-3.59***	-3.15***	-3.03***
Age, years	0.04	-0.09*	-0.10	0.06	0.12**	0.04
Gender, male	0.01	-0.22	-0.39	-0.30	-0.96	-0.38
R^2	0.45	0.15	0.41	0.49	0.41	0.51
Sleep Onset Delay (1-3)	**-0.32**	**-0.14**	**-0.49**	**-0.31**	**-0.40**	**-0.16**
DS presence	-5.10***	-1.45**	-4.47***	3.81***	-3.27***	-3.26***
Age, years	0.05	-0.06	-0.04	0.11**	0.13***	0.07*
Gender, male	-0.10	-0.52	-0.77	-0.55	-1.15***	-0.54***
R^2	0.46	0.12	0.35	0.45	0.42	0.48
Sleep duration (3-9)	**-0.30****	**-0.19**	**-0.35****	**-0.18***	**-0.21***	**-0.19****
DS presence	-5.34***	-1.44**	-4.30***	3.59***	-3.17***	-3.19***
Age, years	0.04	-0.06	-0.04	0.10**	0.14***	0.07*
Gender, male	-0.03	-0.55	-0.95	-0.75	-1.22***	-0.65*
R^2	0.50	0.14	0.36	0.45	0.42	0.50
Sleep anxiety (4-12)	**-0.18**	**-0.32*****	**-0.55*****	**-0.23****	**-0.10**	**-0.24*****
DS presence	-4.98***	-1.41***	-4.21***	3.72***	-3.21***	-3.11***
Age, years	0.03	-0.10**	-0.10*	0.07	0.11**	0.04
Gender, male	0.04	-0.38	-0.69	-0.50	-0.99**	-0.52
R^2	0.46	0.17	0.41	0.46	0.41	0.52
Night Wakings (3-9)	**-0.44****	**-0.31***	**-0.53****	**0.41*****	**-0.25**	**-0.28****
DS presence	-4.80***	-1.25**	-4.14***	3.53***	-3.10***	-3.09***
Age, years	0.03	-0.07	-0.08	0.08*	0.12**	0.05
Gender, male	-0.13	-0.55	-0.09	-0.56	-1.16***	-0.50
R^2	0.48	0.14	0.37	0.48	0.42	0.49
Parasomnias (7-21)	**-0.21***	**-0.30*****	**-0.24***	**-0.22****	**-0.16**	**-0.18****
DS presence	-5.02***	-1.04*	-3.88**	3.31***	-2.89***	-2.87***
Age, years	0.03	-0.07	-0.05	0.09**	0.12***	0.06*
Gender, male	0.16	-0.36	-0.71	-0.54	-1.07**	-0.52
R^2	0.49	0.19	0.35	0.46	0.41	0.50
SDB (3-9)	**-0.40*****	**-0.24****	**-0.38****	**-0.26****	**-0.36*****	**-0.28*****
DS presence	-4.80***	-1.32**	-4.25***	3.61***	-3.01***	-3.07***
Age, years	0.05	-0.07*	-0.06	0.09**	0.13***	0.05
Gender, male	0.09	-0.23	-0.47	-0.39	-0.84*	-0.33
R^2	0.51	0.16	0.40	0.47	0.44	0.53
Daytime sleepiness (8-24)	**-0.17***	**-0.13**	**-0.21***	**-0.17****	**-0.07**	**-0.09**
DS presence	-4.82***	-1.31**	-4.12***	3.52***	-3.11***	-3.04***
Age, years	0.06	-0.05	-0.02	0.12***	0.14***	0.08**
Gender, male	0.01	-0.36	-0.69	-0.44	-1.08**	-0.51
R^2	0.46	0.12	0.34	0.46	0.40	0.47
Total CSHQ (33-99)	**-0.06****	**-0.06****	**-0.12*****	**0.08*****	**-0.04**	**-0.05****
DS presence	-4.74***	-1.19**	-3.67***	3.38***	-3.08***	-2.89***
Age, years	0.04	-0.07	-0.07	0.08**	0.12**	0.06
Gender, male	-0.12	-0.45	-0.85	-0.54	-01.12**	-0.61*
R^2	0.47	0.15	0.4	0.49	0.42	0.51

*** p≤0.01; ** p>0.01 & p≤0.05; * p>0.05 & p≤0.10

Table 2.8. Coefficients and significance for life habit outcomes in multivariable regression models. All explanatory sleep variables (CSHQ subscales) in model, controlled for DS status, age and gender

Outcomes: → **Explanatory variables**	**Mealtimes**	**Fitness**	**Personal Care**	**Communication**	**Home life**	**Mobility**
DS presence	-2.06**	-1.28**	-3.10**	-3.80**	-1.51**	-3.54**
Age, years	0.01	-0.05	0.15**	0.07	0.04	0.07
Gender, male	-0.53	-0.18	-0.35	-0.55	0.18	0.46
Bedtime resistance	-0.15	-0.22	-0.37**	0.21	0.04	0.24
Sleep onset delay	0.18	-0.27	0.01	-0.06	0.10	0.45
Sleep duration	-0.04	0.21*	-0.05	-0.10	0.00	0.07
Sleep anxiety	0.00	-0.07	0.04	-0.19	-0.06	-0.34*
Night wakings	-0.17	-0.28	0.05	-0.30	0.04	-0.15
Parasomnias	-0.14	-0.09	-0.08	0.06	0.14	0.04
SDB score	-0.26	-0.29**	-0.31**	-0.01	-0.55**	-0.18
Daytime sleepiness	-0.01	0.01	0.13	0.00	0.03	-0.07
R2	0.38	0.35	0.55	0.47	0.41	0.45

Outcomes: → **Explanatory variables**	**Responsibilities**	**Relationships**	**Community Life**	**School**	**Recreation**	**Total Life-H**
DS presence	-4.76**	-0.82	-3.90**	-3.08**	-2.66**	-2.75**
Age, years	0.02	-0.08	-0.14**	0.04	0.10*	0.02
Gender, male	0.33	-0.19	-0.44	-0.14	-0.72	-0.27
Bedtime resistance	0.19	-0.06	-0.19	-0.24	0.07	-0.07
Sleep onset delay	-0.14	0.01	-0.48	-0.35	-0.19	-0.07
Sleep duration	-0.09	-0.04	-0.06	0.06	0.04	0.00
Sleep anxiety	-0.16	-0.04	-0.35	0.05	-0.05	-0.11
Night wakings	-0.45**	-0.24	-0.39	-0.35*	-0.33	-0.21
Parasomnias	0.03	-0.15	0.24	0.01	0.00	0.03
SDB score	-0.33*	-0.14	-0.40*	-0.29*	-0.35**	-0.26**
Daytime sleepiness	-0.05	0.01	0.02	-0.04	0.01	0.00
R2	0.56	0.19	0.46	0.50	0.44	0.55

** $p \leq 0.05$; * $p > 0.05$ & $p \leq 0.10$

Chapter 3

Associations between Sleep Disordered Breathing Symptoms, Sleep Duration, Obesity and Physical Activity in Children and Adolescents with Down Syndrome

Associations between sleep disordered breathing symptoms, sleep duration, obesity and physical activity in children and adolescents with Down syndrome

Abstract

Objectives: The purpose of this study is to describe the prevalence of sleep disordered breathing symptoms (SDBS), sleep duration patterns, physical activity patterns and obesity and the associations thereof in one sample of children; most with Down syndrome (DS).

Design: Cross-sectional study with an Internet sample

Setting: Online survey filled out at home

Participants: 110 parents of children with DS and 29 parents of children with typical development (TD) age 5 to 18 years.

Interventions: N/A.

Measurements and Results: Children's sleep habits questionnaire was used to collect information about sleep disordered breathing symptoms and sleep duration. The children's physical activity questionnaire was used to collect information about light, moderate and vigorous physical activities during the previous seven days. As expected, a higher proportion of children with DS had SDBS present (33.00% versus 11.54% in children with TD; $p=0.031$). Multivariable regression modeling was used to assess the associations between sleep variables, physical activity and obesity. Presence of SDBS was associated with an average 38-minute shorter sleep duration ($p=0.005$). No relationship was found between SDBS or sleep duration with physical activity. Significant associations were found between hours of moderate to vigorous physical activity and obesity (odds ratio [OR] = 0.87; $p<0.01$); and between presence of SDB symptoms and obesity (OR=5.78, $p<0.01$), in all children with and without DS.

Conclusions: Intervention to reduce obesity in youth with Down syndrome may reduce the occurrence of sleep disordered breathing and improve health and quality of life.

Introduction

In epidemiologic studies poor quality sleep has been linked to health-related quality of life (1, 2); and in experimental studies, poor quality sleep has been linked with diminished academic performance, cognitive and learning deficits, and inattentive behaviors evident in children (3-5). One reason for inadequate and poor quality sleep in children is sleep disordered breathing (SDB). SDB is a class of sleep disorders related to respiratory problems during sleep. The most common of these disorders is obstructive sleep apnea (OSA). OSA is defined as "an absence or reduction in airflow in the upper airway despite ongoing respiratory effort, frequently in combination with paradoxical breathing efforts and/or snoring (6)." OSA has recently been linked with short sleep duration in adults (7). In children SDB is linked with parasomnias (8), and SDB has also been directly associated with academic performance in school children (9). In addition, health problems associated with SDB include complications in cerebrovascular and cardiovascular function, and obesity (10-12). Although the long-term effects of SDB on cardiovascular and cerebrovascular functions are largely unknown in children, subclinical markers of cardiovascular disease, systemic and pulmonary hypertension, have been associated with SDB in children (11). It is well established that obesity is a risk factor for both cardiovascular disease and SDB. In particular, recently it has been suggested that a synergistic relationship exists between obesity and SDB in children that exacerbates subsequent cardiovascular problems (11). Bhattacharjee and colleagues assert that, even in non-obese children with SDB, this synergistic interaction may lead to symptoms that mimic characteristics of obese children and lead to the same systemic inflammatory responses that are associated with obesity, such as insulin resistance and hypertension (11). This scenario is concerning for all children with SDB but even more so in children with Down syndrome (DS) because of the increased risk for both obesity and SDB in this population.

The prevalence of SDB is estimated to be 1% to 2% in all young children (13). In adolescents symptoms of SDB have been estimated to be 4% (14). The prevalence of SDB and the symptoms of SDB have been reported to be higher in children with DS than children with typical development (TD). Parent reports of symptoms of SDB in children with DS range between 45% to 60% for at least one symptom of SDB, for example, snoring or gasping for breath while asleep (15, 16). Polysomnographic studies of children with DS have documented SDB prevalence of 54% to 90% in clinical samples, and 24% to 59% in community samples (17).

Children with DS are also at greater risk for obesity, and in clinical samples have exhibited higher rates of overweight and obesity than children with TD (18). A few factors may influence the risk of obesity in DS: short stature; delayed physical and cognitive development acting as barriers to learning new skills enabling routine participation in sports and physically active games (19); lower resting metabolic rate and general hypometabolism (20). Another reason for limited physical activity (PA) in DS may be pulmonary hypertension (PH). From infancy to adulthood children with DS are at higher risk for PH than children with TD (21). PH is associated with lower exercise endurance and tolerance in children (22). Indeed it has been suggested that PH is a result of SDB in DS (23). A recent study of PA patterns in children with DS found that most were not meeting the recommended daily minimum 60-minute recommended moderate to vigorous PA (19, 24).

Patterns of PA, obesity risk, SDB risk, and other sleep problems in DS have been studied independently and descriptively. A few studies have considered pairwise associations; for example, obesity with SDB (18), and PA with obesity (19). No studies have quantified these risks concurrently in the same sample of children with DS to determine the associations of these factors in one group of children. It is important to assess these associations within one sample because the inter-relationships between factors observed within the same group of children could point to modifiable underlying mechanisms with reduced interference of confounding factors, which could affect the results if samples are different. Properly identified modifiable mechanisms could be intervened with to effect a desirable change in sleep outcomes. The purpose of this study was to describe sleep disordered breathing symptoms (SDBS), sleep duration patterns, physical activity patterns and obesity, and the associations thereof in a sample of children mostly with DS, and a small proportion without DS for comparison.

The theoretical framework of this study is adapted from the conceptual model proposed by Lee et al. (25). Figure 3.1 shows the adapted model for the context of this study focusing on the relationships investigated here. The Lee et al. model postulates that sleep loss, due to sleep deprivation and sleep disruption, leads to adverse health outcomes and daytime consequences, such as impaired physical and mental function, manifested as less physical activity, fatigue, impaired short-term memory and problem solving. A child with disrupted sleep, regardless of etiology, may be excessively tired and sleepy during the day leading to poor performance in school and less participation in after school sports activities, further leading to obesity and subsequent SDB. Specifically, within this study the relationships between SDBS, sleep duration, physical activity and obesity were examined. SDBS was hypothesized to be associated with shorter duration of sleep in children; SDBS and shorter duration of sleep were hypothesized to be associated with both obesity and lower amount of PA in children with DS.

Key Questions and Hypotheses:

I. What are the descriptive characteristics of physical activity in children with DS and how do they compare with a sample of children with TD? What proportion of children with DS meets the daily amount of PA recommended by the Centers for Disease Control and Prevention (CDC)? What are the factors that influence meeting the PA recommendation?

II. What is the association of SDB symptoms with duration of sleep in children?

Hypothesis 1: Children with higher SDBS scores have shorter sleep duration.

III. What are the relationships of SDBS and sleep duration with PA?

Hypotheses 2a and 2b: lower amount of moderate to vigorous PA (MVPA) is associated with more SDB symptoms and shorter sleep duration.

IV. What is the relationship of obesity with PA?

Hypothesis 3: lower amount of MVPA is associated with obesity.

V. What is the relationship of SDBS with obesity?

Hypothesis 4: SDBS is associated with presence of obesity.

These questions are important to address because promoting health and fitness is an issue of health equity social justice for all children, and particularly for those with DS. It is critical to find ways to improve sleep outcomes in children with DS. Better sleep outcomes are related to better accomplishment of daily life habits in children with DS (Churchill, 2013, chapter 2 of dissertation). Because of developmental, cognitive and physical delays, children with DS are at a disadvantage for accomplishing their daily life habits and activities compared with children with TD, it is important to determine how to improve sleep so that accomplishment of daily life habits can be maximized to the extent possible among children with DS. For example, are increasing PA and reducing obesity venues that could impact SDB and sleep duration in DS? If so, then new interventions could be tested in children with DS to alter PA and obesity patterns in order to improve sleep and ultimately improve the accomplishment of daily life habits.

Methods

This Internet survey study was approved by the Institutional Review Board at the University of Washington. All participants received a consent form by e-mail and provided electronic consent prior to completing the survey. The study was a cross-sectional survey of parents of children with and without DS, ages 5 to 18 years.

Participant Recruitment and Data Collection

Survey announcements were posted on an English speaking international listserv for a Down syndrome support group with a membership of approximately 700 members at the time of announcement. The announcement was also posted on the U.S. National Down Syndrome Society's "Directory of Current Studies," and the greater Seattle area DS listserv and newsletter. Recipients of the announcement were encouraged to forward the announcement to other families in their social circles. Parents of children with DS were asked to forward the announcement to their friends and family with children with TD. Those interested in participating were asked to contact the investigator by phone or e-mail. Each parent could participate only once, reporting on only one of their children. Siblings were not allowed to be reported on by the other parent. A drawing, at the end of the survey, for seventy-five $25 gift cards, was offered as an incentive for participation. Recruitment was carried out from June to November of 2012. Parents reported the

DS or TD status of their child as well as the birth month and year of the child, the only qualifying requirements for participating in the study in addition to English language ability. No recruitment quota was established, but it was expected that at least 100 parents would enroll during the recruitment phase, with a DS:TD ratio of 3:1.

Once a parent agreed to participate in the 45 minute Internet survey, a private non-transferable survey link was sent to them by e-mail. No identifying information was collected within the survey and the data were anonymous. Once all survey data were collected contact information (e-mail address) was deleted. Research Electronic Data Capture (REDCap), a secure web-based application for electronic data collection and management (26), hosted at the University of Washington, was used for developing the Internet data collection tool and database.

Parents were instructed to complete the survey in one session, but were informed that once started, the survey could be completed later if necessary, via a private reentry code given to the participant when exiting an unfinished survey. Among the 155 enrollees who were set up with a survey link 139 (90%) participated by accessing the survey. Enrollees who had not opened the survey or had left it unfinished received up to three reminders before the survey closing date, unless they had requested withdrawal. Among the 16 enrollees who never opened the survey two made contact and requested to withdraw due to lack of time. Among the 19 participants who had partial surveys, six contacted the investigator with the following reasons for incompletion: three due to lack of time, two had computer problems, and one did not like the survey questions. Parents who contacted the investigator about computer problems were offered a hard copy of the survey with postage paid return envelopes; one parent accepted and returned the completed survey by post which was then entered by study personnel. The final analytic sample size was 98-104 in the DS group and 23-25 in the TD group, depending on missing values for specific variables in analyses. At the most in any single analysis a maximum of 11.5% missing data was allowed. Missing values were not replaced in any of the analyses.

Measures

Demographics, health characteristics and obesity

Parents completed questions about country of residence, relation to child, gender, age, height and weight of child, presence of siblings, frequency of exposure to tobacco smoke, and if the child had ever had any of the following: sleep study, diagnosis of sleep apnea, tonsillectomy, use of continuous positive airway pressure (CPAP) device, heart surgery, or diagnosis of gastrointestinal disease. Parent-reported height and weight were used to calculate body mass index (BMI) percentile using the CDC's Children's BMI Tool for Schools (27). The same age- and gender-specific BMI standard was used for children with and without DS. Underweight, normal, overweight, and obese weight categories were defined as follows: underweight, $\leq 5^{th}$ BMI percentile; normal weight, $>5^{th}$ and $<85^{th}$ BMI percentile; overweight, $\geq 85^{th}$ and $<95^{th}$ BMI percentile; and obese, $\geq 95^{th}$ BMI percentile. (28)

Sleep characteristics

Sleep characteristics of children were determined using the well-established Children's Sleep Habits Questionnaire (CSHQ) (29), which has been used in numerous studies of children's sleep, including studies of children with DS (15, 16). The CSHQ is a 45-item questionnaire of which 33 items are grouped into 8 conceptual domains (subscales). One domain from the questionnaire was used in this study, SDB symptoms. This domain was selected because SDB is a common sleep problem in DS (30, 31), and is associated with the accomplishment of important daily life habits and activities (Churchill 2013, Chapter 2 of this dissertation). Three CSHQ items ask about the frequency of SDB symptoms: "snores loudly," "stops breathing," and "snorts and gasps." Each item is rated from 1 to 3 respectively as "rarely, 0-1time a week," "sometimes, 2-4 times a week," or "usually, 5-7 times a week." The SDBS subscale ranges from 3 to 9 points, where a higher score reflects more sleep disturbance by SDBS. For logistic regression analyses the SDBS score was dichotomized based on previously-published clinically-acceptable cut-off point of $\geq$5 (32). A score of 5 points for SDBS signifies the presence of at least one symptom 5-7 nights a week, or at least two symptoms 2-4 nights a week each. While this cut-off point may not identify all cases of SDB that may have been identifiable by PSG, it may identify some subtle but clinically important limitations in airflow. Subtle symptoms are important, as mild cases of OSA may have important long-term consequences in health (6, 33). Analyses using SDBS were performed using both the continuous and dichotomous variable for SDBS in parallel. This methodology was used to demonstrate if the relationship and the direction of association was robust enough to be unaffected by minor change in variable definition (continuous versus dichotomized) given that measurements were subjective. To specify whether the continuous or dichotomized SDBS variable is being reported on in the manuscript, the continuous SDBS variable is referred to as "SDBS score" and the dichotomized SDB variable is referred to as "presence of SDBS."

The CSHQ includes weekday and weekend bed-times, wake-times, and duration of sleep. For analyses involving duration of sleep, minutes were calculated as fractions of an hour and then were converted back to minutes for consistency in reporting. An average daily number of hours of sleep was calculated by: [(weekday sleep hours x 5) + (weekend sleep hours x 2)] / 7. For descriptive purposes, average sleep duration was compared between two age groups: 5 to 12 years, and 13 to 18 years. This age grouping was based on previous studies of children with DS and children with TD using the CSHQ (16, 29), and reflects the age-related developmental changes in sleep.

Physical Activity

Physical activity was assessed using the Children's Physical Activity Questionnaire (CPAQ) which is designed for children and adolescents with TD, and completed by the parent. (34) There are no published accounts of the CPAQ having been used in children with DS. The original questionnaire has 47 activity items; two items were added by the investigator, Wii Fit and horseback riding, because these two items have become activities of choice for some children with developmental delay (DD) including DS. Wii Fit is a safe indoors mechanism of PA that has become common in the recent years (35); and horseback riding has been advocated as beneficial and therapeutic for children with DD (36). In addition, opportunities were provided for parents to add "other activities" on the questionnaire. For each activity the parent indicated the frequency and the amount of time spent on the activity on weekdays and weekends "for the past 7 day." Each of the activities was assigned a metabolic equivalent of task (MET) value according to well-established published values (37, 38). The activities were then grouped into 3 categories: light activities (LA), moderate PA (MPA), and vigorous PA (VPA). Table 1 shows the CPAQ questionnaire items and their categorization into three MET groups. For determining the proportion of children who the met the CDC guideline for PA, the MPA and VPA categories were combined to make the moderate/vigorous PA (MVPA) category. Weekly minutes for each type of activity and for each category of activities, LA, MPA, VPA, and MVPA, were calculated. The daily minutes of MVPA were calculated, and this variable was dichotomized to assess whether the children in this study met the guideline of at least 60 minutes of daily MVPA.

Statistical Analysis

Stata software version 12.1 (39) was used for analysis. Statistical tests were two-sided with significance level set at probability (p) <0.05. Descriptive demographic and health characteristics of the sample were summarized by listing means and standard deviation for continuous variables and frequencies for categorical variables. These characteristics were compared between groups of children with and without DS using t-tests for continuous variables and chi-square tests for categorical variables. SDBS and sleep duration characteristics derived from the CSHQ and activities derived from the CPAQ questionnaire were also summarized and compared between the two groups. T-tests were used to compare the minutes of PA between the groups DS and TD, for individual activities as well as MET categories of activities, LA, MPA, VPA and MPVA. Chi-square tests were used to compare the proportion of parents reporting each activity between DS and TD.

Ordinary least squares (OLS) and logistic regression analyses were performed to assess associations between variables of interest. The goal of this assessment was to describe trends and to test the hypotheses that: more SDB symptoms are associated with shorter sleep duration; more SDB symptoms are associated with obesity and less MVPA; longer sleep duration is associated with more MVPA; and, that lower amount of PA is associated with obesity in children with DS. Multivariable regression models were adjusted for DS status, age and gender in all cases. Age is important in analyses of sleep and activity as both sleep and activity vary developmentally by age. Gender is also important to control for as there could be differences in PA and/or sleep patterns between boys and girls; and particularly in this study sample, because of the skewed gender distributions in the DS and TD groups. Logistic regression was used when the outcome of interest was dichotomous: SDBS presence, meeting the CDC guideline for

MPVA, and obesity. OLS regression was used for continuous outcome variables such as SDBS score and minutes of MPVA. In multivariable regression analyses where the outcome was MVPA, or SDBS, tonsillectomy and heart surgery were controlled for in the model, as these factors may influence physical activity and SDBS. In all multivariable regression analyses interactions between the outcome variable with DS status, age and gender were examined.

Results

Demographic, Health and family characteristics

Participants were parents who responded to questions about their child who lived with them at the time of the survey. The majority of respondents were mothers from the United States. All children reported on were ambulatory. Table 2 summarizes the sample characteristics. The samples of children with and without DS were balanced with respect to presence of younger and older siblings and exposure to cigarette smoke. A majority of children with DS were male while the majority of the TD sample was female. As expected, children with DS were more likely to be overweight or obese, to have ever had a sleep study, and/or have ever been diagnosed with sleep apnea; and were more likely to have ever had tonsillectomy or heart surgery. Among children with DS 15% had used a continuous positive air pressure (CPAP) device at some point, where none of the children with TD had ever used such device. None of the children with TD had ever had a sleep study, been diagnosed with sleep apnea or had heart surgery.

Sleep Characteristics

Two sleep variables were used in this study, sleep duration and SDBS. Table 3 summarizes sleep duration and SDBS by DS status and by age group. Younger children with DS, ages 5 to 12 years, had a consistent number of hours of sleep during the week; there was no difference between weeknight and weekend hours of sleep. On the average, younger children with TD had slightly longer sleep duration on weekend, ~21 minutes, but overall younger children with DS and TD did not differ significantly in the number of hours of sleep averaged over the week. Among teenagers, those with DS had more consistent sleep hours during the week, i.e. the variation between weeknight and weekend hours of sleep was smaller, ~19 minutes, versus 92 minutes in teenagers with TD. Teenagers with DS had significantly longer hours of sleep than teenagers with TD over the entire week (average of 55 minutes longer, p-value=0.011), largely due to earlier average bedtime on weeknights and weekends.

As expected, SDB symptoms were significantly more pronounced in children with DS compared to children with TD (p-value=0.006) and teenagers with DS had on the highest SDBS scores. Thirty-three percent of all children with DS had a SDBS score $\geq$5 compared to 12% of Children with TD. Within ages 13-18 years, 47% of those with DS and 8% of teens with TD had SDBS scores $\geq$5.

The association between SDBS and sleep duration *(Hypothesis 1)*

Figure 3.2 shows the mean SDBS score by average hours of nightly sleep for children with DS and children with TD. In both groups, children with higher SDBS scores had shorter sleep duration. In regression analysis where average hours of sleep was the outcome variable, and SDBS score and DS status were explanatory variables, significant associations were observed between both SDBS and DS status with sleep duration. While children with DS had a higher baseline of average sleep hours, by 34 minutes (p-value=0.037), every point increase in the SDBS score translated into a 9 minute decrease in sleep duration for all children (un-adjusted p-value=0.033). Adjusted for DS status, age and gender, every point increase in SDB score was associated with a 7-minute decrease in sleep duration (adjusted p-value=0.073). Age was a significant factor in multivariable analysis, with a 7-minute decrease in sleep duration for every year increase in age (adjusted p-value <0.001). DS status and gender were statistically non-significant (Table 3.4). In multivariable analysis where SDBS presence was used as a dichotomous variable, the presence of SDB symptoms (SDB score $\geq$ 5) was associated with a 38 minute decrease in sleep duration (adjusted p-value=0.005). Age remained a significant factor, with older children experiencing shorter duration of sleep (Table 3.5).

Physical activity characteristics

Parents reported on the frequency and amount of time children engaged in various activities in the previous 7 days. The most frequently reported activities—activities reported by more than 5 parents of children with DS, are summarized in Table 3.6. While all children with DS, or TD, spent more time on light activity (LA) than moderate or vigorous physical activity (MPA or VPA) during the week, children with TD spent significantly more time on VPA per week (p-value < 0.001) than children with DS. Weekly time spent on LA was greater for children with DS by more than 2 hours on the average. The average weekly minutes of MPA were almost identical between the two groups, with a 10 minute difference. Among light activities, amount of time spent on some sedentary activities differed significantly between children with DS and children with TD. A significantly greater amount of time was spent watching TV among children with DS, with an average of 10 hours per week, versus 5 hours and 30 minutes average per week for children with TD. On the other hand, children with TD spent significantly more time on homework, 7 hours and 50 minutes per week versus 3 hours and 33 minutes for children with DS.

Proportion of children meeting the daily recommended amount of MPVA and related factors

Given the subjective CPAQ measures of PA, more than 60% of the children in this study met the CDC's minimum 60 minutes of daily MVPA guideline—children with TD at a rate of

65% and children with DS at 61%, not a statistically significant difference. To assess whether meeting the 60-minute-MVPA criteria was related to other factors, multiple logistic regression was performed to evaluate the roles of age, gender, sleep duration, SDBS, having had heart surgery, or tonsillectomy. In both univariable and multivariable logistic regression children with DS had lower odds of meeting the criteria although these relationships were not statistically significant. Older age and male gender were positively associated with meeting the 60-minute-MVPA criteria, but were not statistically significant. Having had a tonsillectomy was a statistically significant factor in meeting the daily 60-minute MPVA in all children, with an odds ratio (OR) of 2.1 (p-value=0.051) in unadjusted analysis and an OR of 2.7 (p-value=0.028) in the multivariable adjusted model. Tonsillectomy was also evaluated in an OLS multivariable regression model with the continuous variable daily minutes of MVPA as the outcome. The coefficient of regression was a 24-minute increase in daily MVPA if the child had a tonsillectomy (p-value=0.060). Regression tables for these analyses can be found in Appendix 3.A. Among children with DS, 70% of those who had a tonsillectomy met the 60-minute MPVA criteria, versus 49% of those who had not had a tonsillectomy (n=104, χ^2=4.87, p-value=0.027).

The relationship of sleep duration, and sleep disordered breathing symptoms with physical activity *(Hypotheses 2a and 2b)*

The associations of SDBS and sleep duration with LA, MPA, VPA and MVPA were evaluated in unadjusted models and in multivariable (adjusted) OLS regression models. Multivariable models were adjusted for DS status, age and gender. Contrary to hypotheses, there were no associations between SDBS and daily minutes of LA, MPV, VPA or MVPA in any of the adjusted or unadjusted models (all p-values > 0.10). No associations were found between sleep duration and PA variables (all p-values > 0.10). Multivariable regression tables for these analyses can be found in Appendix 3.B. In further multivariable analysis, children with DS had significantly increased probability of having less VPA (p-value=0.003), and had higher levels of LA than children with TD (p=0.075), with girls being more likely to have a larger amount of LA than boys (p=0.071). These findings were unrelated to sleep duration and SDBS, and the analysis controlled for age, gender, SDBS score, sleep duration, heart surgery and tonsillectomy. SDBS was first used in models as a continuous variable and then parallel logistic regression analyses were performed with SDBS presence as a dichotomous variable with similar results.

The relationship of obesity with Physical Activity *(Hypothesis 3)*

Table 3.7 summarizes the results of multivariable logistic regression for obesity outcome (BMI percentile $\geq$95) among all children and within children with DS. Among all children, with or without DS, every hour increase in weekly MPVA was associated with a 13% decline in the odds of being obese (p-value=0.006). This finding is in agreement with the hypothesis that lower amounts of PA are associated with obesity. This analysis controlled for age and gender and these factors were not statistically significant.

The relationship of SDBS with obesity *(Hypothesis 4)*

Presence of SDBS (the proportion of children with SDBS score of $\geq$5) was higher in overweight and obese children with or without DS. The mean SDBS score was also higher in overweight and obese children. Figure 3.3 and 3.4 show the distributions of SDBS presence (% of children), and SDBS score means by weight category (normal weight, overweight, and obese), and by DS status. Three children, two with DS and one with TD, were underweight ($\leq 5^{th}$ age- and gender-specific BMI percentile) and were not included in the graphs in Figures 3.3 and 3.4 (see Discussion). Presence of SDB symptoms was modeled in multivariable logistic regression using the dichotomous SDB variable. Among all children (OR=5.78, p=0.002), and among children with DS (OR=5.50, p=0.005), BMI percentile of $\geq$ 95 for age and gender, was significantly associated with SDBS presence. Within children with DS (OR=6.97, p=0.023), and all children (OR=3.48, p=0.050), male gender was significantly associated with presence of SDB symptoms. Older age was also positively associated with SDBS presence among all children (OR=1.12, p=0.065). This finding is in agreement with the hypothesis that obese children have greater rates of SDBS. Of note, having had a tonsillectomy was positively associated with the presence of SDBS (OR=4.80, p=0.004). Table 3.8 summarizes these results. The continuous SDBS score variable was used as dependent variable in parallel OLS multivariable regression analysis, controlling for DS status, age and gender; and it showed similar results (coefficient for obesity 0.74 in all children, p-value=0.024).

Discussion

The present study found several significant associations pertaining to sleep duration, SDB symptoms, PA, and obesity, in this sample of children most of whom had DS (80%). First, SDBS was associated with shorter duration of sleep in all children with and without Down syndrome. Children with DS had longer sleep duration to begin with, likely resulting from earlier bedtime than children with TD. Also, children with DS appeared to have more regularity in bedtime and sleep duration across the entire week, unlike children with TD who had more variable sleep duration and bedtime between weekends and weekdays. This stability is a positive sleep hygiene practice for children with DS as it has been suggested that weekday-weekend variability in sleep of children could be related to obesity and reduced PA (40). Based on previous findings from this dataset (Chapter 2 of this dissertation) SDB appears to be the backbone of sleep problems in DS, as many of the sleep problems identified by the CSHQ are strongly associated with SDB, and in multivariable analysis SDB prevails over other sleep problems.

What can be done to reduce SDB in children with or without DS? There is good evidence that adenotonsillectomy at least reduces SDB symptoms and sometimes completely resolves the problem (41). In this study there was some indication that tonsillectomy was a factor in better PA performance; perhaps because tonsillectomy reduced SDB symptoms which may have reduced pulmonary hypertension, and made it easier to be physically active. However, tonsillectomy was also associated with the presence of SDBS (Table 3.8), perhaps indicating that tonsillectomy had been performed because of SDB, although it did not completely resolve it; highlighting again, the need for continued monitoring for SDB after surgical intervention. When SDB is diagnosed, various treatments may be considered to decrease airflow restriction and improve breathing ease during sleep. Treatment options include the use of a continuous positive air pressure (CPAP) device, tonsillectomy, position therapy, nasal decongestion, or a combination of these treatments. Often continued monitoring and treatment with CPAP is necessary after tonsillectomy (41). Unfortunately CPAP tolerance and adherence is low in all patient populations including children with DS (42). Orthodontic appliances have had some success in children with TD (8), but these may not be tolerable or safe in children with DS.

Apart from invasive or semi-invasive procedures, addressing obesity may be an important way of reducing SDB in children with DS. Preventing and/or reducing obesity can serve as a primary or secondary prevention mechanism of SDB in all children. Overweight and obesity are prevalent in children with DS, with 21% and 26% percent prevalence respectively within this study sample. In the general population of children in the U.S. the most recent estimates of overweight and obesity are 15% and 17% respectively, among children of all races between 2 and 19 years of age (43). As expected, this present study found a significant association between obesity and SDB in children with and without DS. It is plausible that by reducing obesity SDB could be reduced in children. However it is important to recall that both underweight and overweight can be risk factors for SDB (44). Within this study there were three children who were underweight (< 5^{th} BMI percentile), two with DS. The two underweight children with DS had SDB scores of 4 and 6 (on a scale of 3 to 9). The prevalence of SDBS score $\geq$ 5 was 22% in children with DS who were within the normal weight category, but this rate climbed to 33% in overweight children, and 52% in obese children with DS. While it is important to probe for SDB in children with DS within all weight categories, there is clear indication that SDB is more prevalent in heavier children.

Physical activity was not directly associated with sleep duration or SDB in this study, but physical activity was strongly associated with reduced obesity. Parents of children with DS reported on a diverse range of activities that their children engage in but the amount of time and/or the intensity with which the child performed the activity may not be adequate to address overweight and obesity. Children with DS had significantly fewer weekly minutes of VPA than children with TD. Engaging in moderate to vigorous physical activity may at times involve some degree of perceived risk for injury and safety, walking to school for example. The percentage of parents that reported their child walked to school was 6% in children with DS, and 26% in children with TD. This discrepancy may reflect this perceived risk among parents of children with DS. While children with TD are usually able to independently walk a few blocks to school by the age of 11 of 12, most children with DS still need supervision at this age. Challenges like this potentially limit routine PA in children with DS, despite their need for increased PA in order to address obesity. This study used the same standard of obesity for children with DS and children with TD. Traditionally Down syndrome growth charts are used to track the growth of children with DS, and it is expected and accepted that children with DS are overweight or obese. Down syndrome does not however have to be a license to be overweight, as this expectation limits focus on preventing obesity with its varied harmful consequences. Indeed, intervention to reduce obesity in Down syndrome may in and of itself reduce the occurrence of ongoing sleep disordered breathing and improve health and quality of life.

This study has several limitations. All data were subjective and by parent report, which can be affected by recall bias, social desirability bias, and measurement error in the case of reporting height and weight. The CPAQ questionnaire is relatively new and has not been tested in parents of children with DS. A major problem in assigning MET values to activities is that MET value depends on a presumed intensity with which a person performs an activity. It helps that exact MET values were not used in this study and broad categories of activities with a wide range of METs were used for analysis; still there is some risk of misclassification of activities that are borderline between LA and MPA or MPA and VPA. Questionnaire reports of activity times are problematic as well. While objective measurement with accelerometers measure activities and their intensity precisely; a parent may put down 60 minutes of soccer time, for example, but the child is not necessarily intensely active for that entire period. Still PA questionnaires are known to provide correct but, lower strength of association when used (45). While measures were subjective, using dichotomous and continuous forms of variables SDBS and MVPA, in parallel analyses, allowed comparison of results using slightly varying definition of variables and demonstrated that the trends were relatively robust and not affected by minor changes in variable format. Therefore, while for the purpose of identifying broad associations the questionnaires are adequate, they are not specific enough to quantify the actual amounts of physical activity, and likely the over 60% report that children met the 60-minute daily MVPA recommendation is an overestimate. The CDC reports a prevalence rate of 29% of high school students meeting the 60 minutes a day recommendation for MVPA (46).

SDB was measured subjectively by questionnaire, using only the symptoms of SDB. Recent reports discuss a problem of under-diagnosis of SDB even by polysomnography (6), thus, using a cut-off point of $\geq$5 helps identify most individuals who may be at SDB risk. One factor that was not considered in this study was the timing of LA, MPA or VPA during the day. This absence of data may be one reason for the finding of no significant association between the quantity of PA and sleep duration in this study. (47) An increase in sleep duration necessarily means decrease in time spent doing something else, possibly PA; therefore it is important to consider the timing and intensity of physical activity objectively. There is need to investigate these questions further in the future.

Finally, the sample for this study, while diverse, was self-selected by those who had access to a computer and the Internet. The prevalence of SDBS score $\geq$5 within the DS sample was 33% and close to expectation; but the 12% prevalence in the TD sample was unexpected. Parents of children with TD who perceived a problem with their child's sleep may have been more likely to become attracted to the study. This is a possibility within the DS sample as well, although the study announcement did not mention sleep "problems." This larger than expected prevalence of SDBS presence in children with TD, enabled the study to draw meaningful and significant conclusions about all children with SDB. The results showed that in some aspects children with and without DS are similar with respect to the underlying mechanisms of SDB.

Conclusions

This study was an effort to examine multiple aspects of sleep problems in DS in the same sample of children. This community living sample included children with DS from several countries and across the United States, contrary to many studies of SDB that use local clinical populations. Therefore this sample is more representative of the general population of children with DS. The presence of the identified associations all in one sample of children strengthens this study by diminishing the effects of known and unknown confounding factors; and showing that underlying mechanisms, PA in reducing obesity, obesity in reducing SDB, and decreased SDB in increasing sleep duration and quality, could be put to work together to improve outcomes in children with DS. Multiple studies, looking at single factors for an outcome, in different samples, cannot establish the interrelatedness of the factors investigated in this study. The present study provides new knowledge and direction for future studies to measure the same associations quantitatively and objectively to confirm or extend results.

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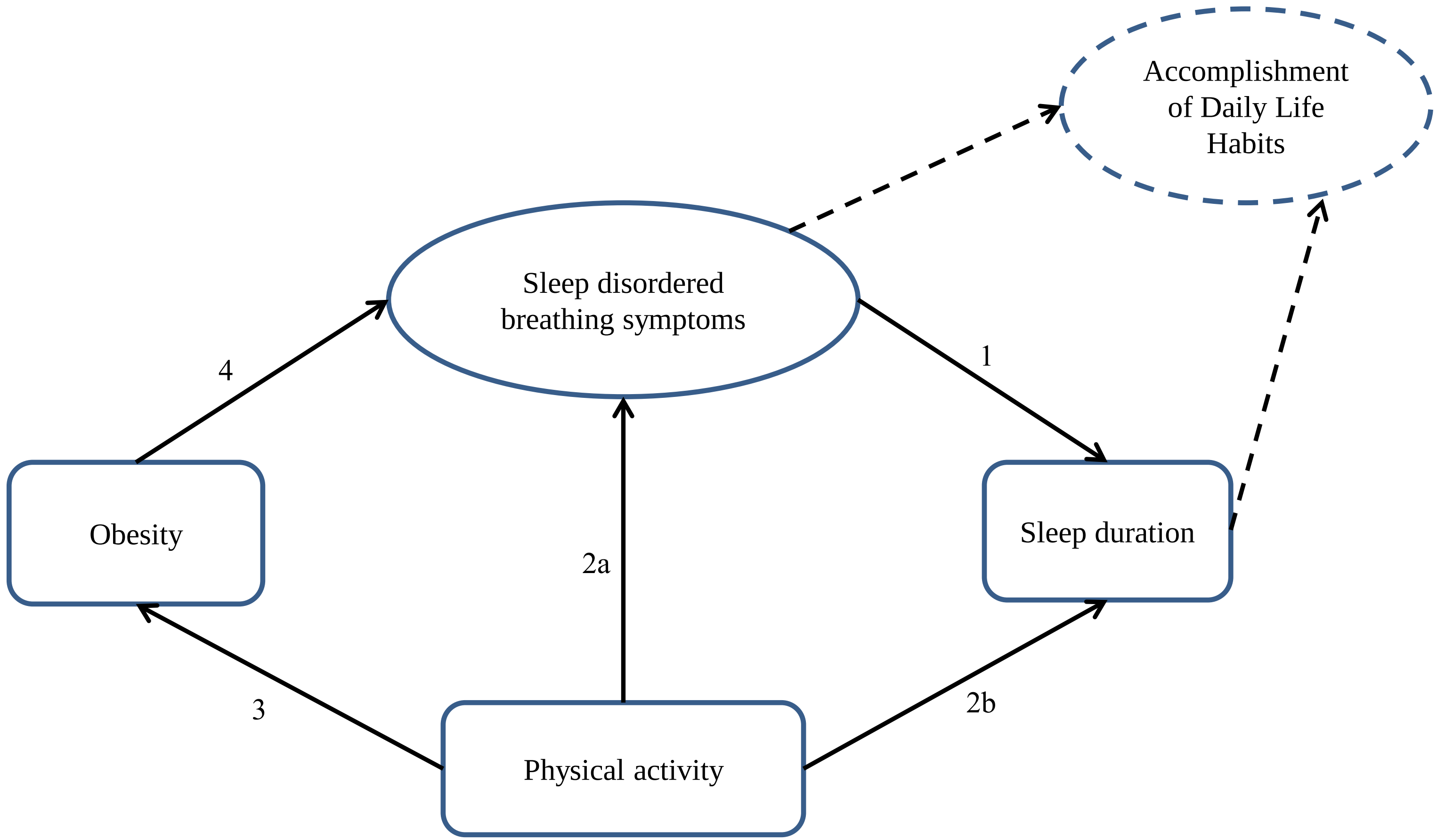

Figure 3.1. Conceptual model showing the relationships investigated in this study. The numbers correspond with the study hypotheses. Arrows point toward dependent variable within each set of two concepts. Dotted lines show related relationships and concepts not within the analysis of this paper.

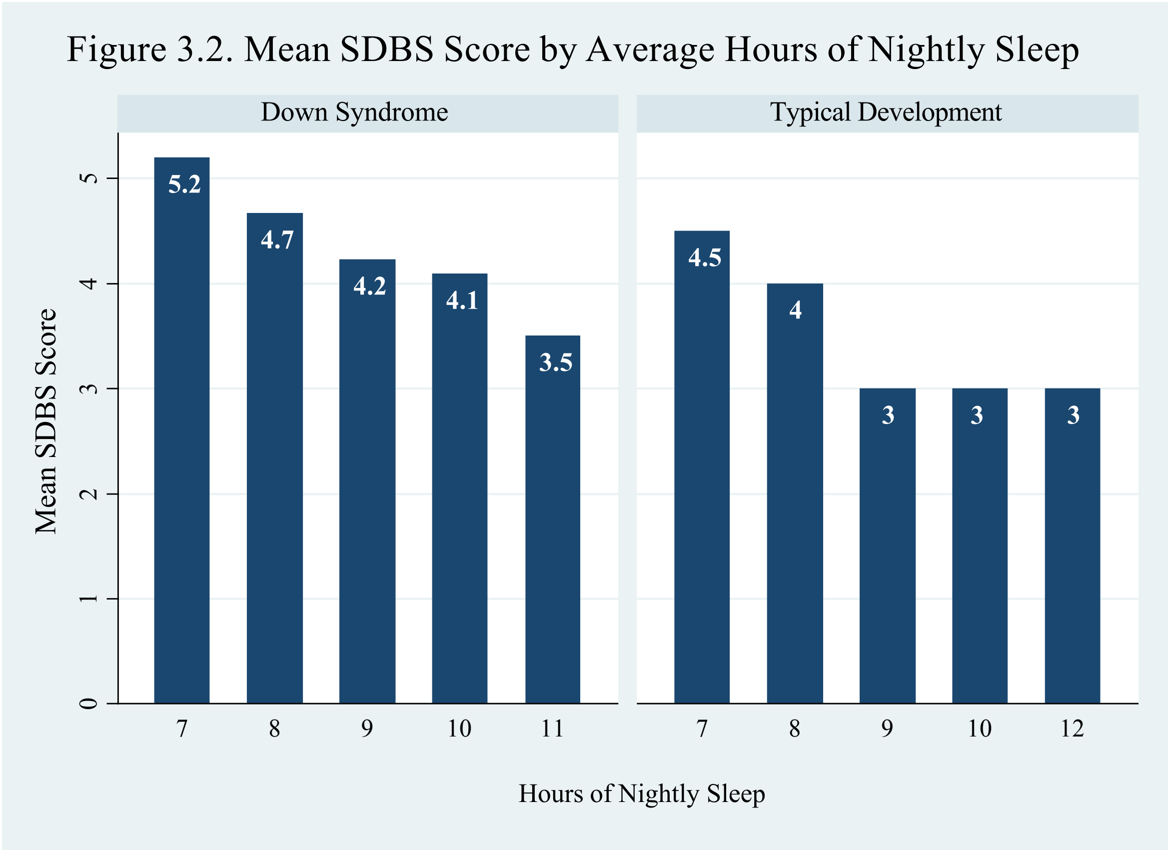
Figure 3.2. Mean SDBS Score by Average Hours of Nightly Sleep
Down Syndrome
Typical Development
Mean SDBS Score
0
1
2
3
4
5
5.2
4.7
4.2
4.1
3.5
4.5
4
3
3
3
7
8
9
10
11
7
8
9
10
12
Hours of Nightly Sleep

Figure 3.3 Mean SDBS Score by Weight Category

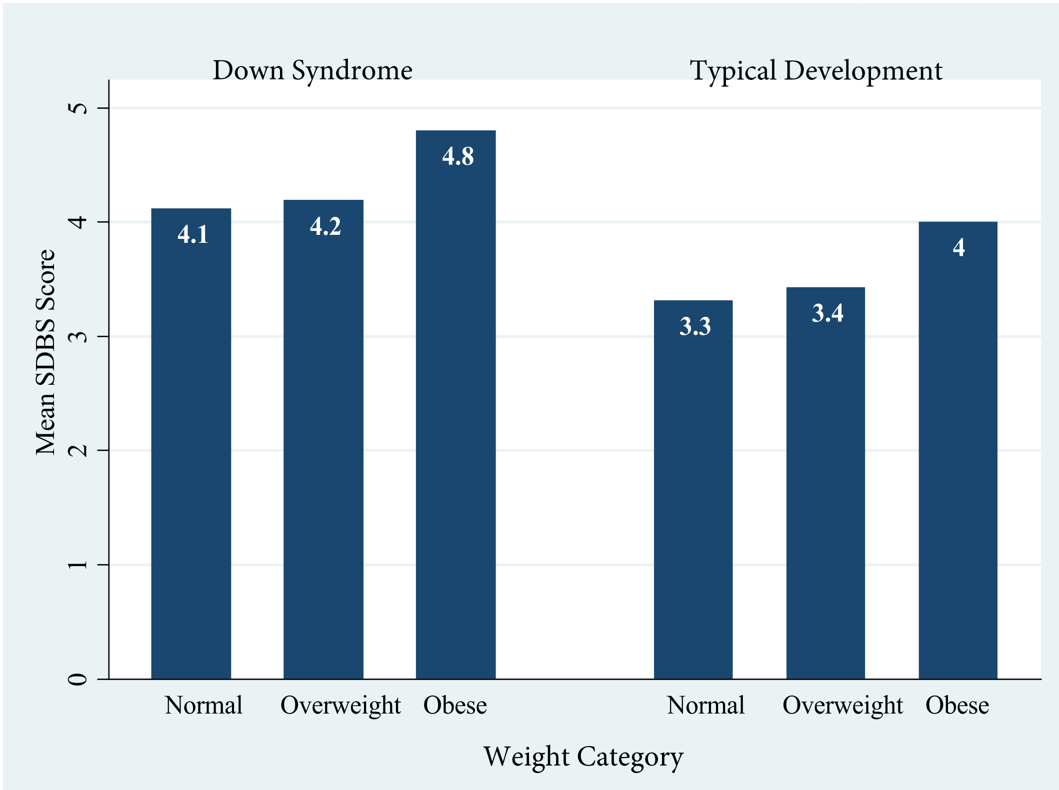

Figure 3.4 Percent of Presence of SDB Symptoms by Weight Category

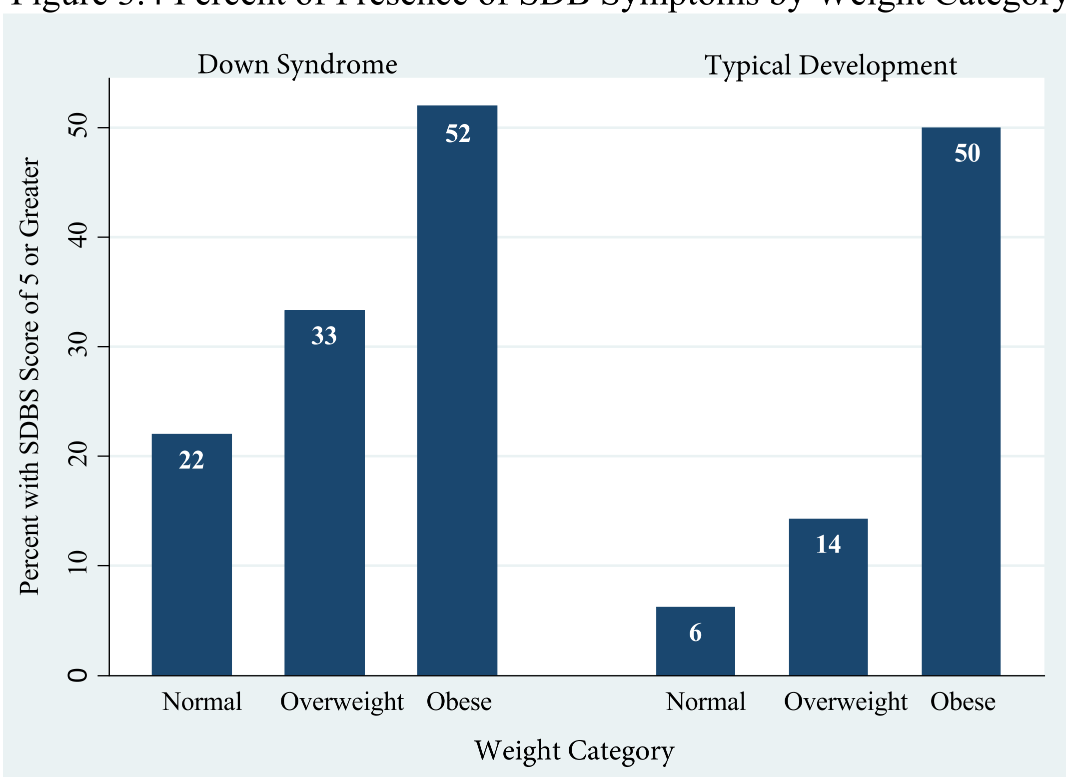

Table 3.1. Metabolic Equivalent of Task (MET) values for activities on the CPAQ questionnaire

Light, < 3 METs	Moderate, 3-6 METs	Vigorous, > 6 METs
Leisure Activities	**Sports Activities**	**Sports Activities**
Play in a play house	Aerobics	Basketball/volleyball
Play with pets	Baseball/softball	Football/Soccer*
	Cricket	Hockey (field or ice)
Activities at School and Home	Dancing	Martial arts
Household chores	Gymnastics	Rugby
Art & craft (e.g. drawing, pottery, painting, sewing)	Netball	Running or jogging
	Swimming lessons	Tennis, Badminton, Squash, other racquet sports
Doing homework	Swimming for fun	
Imaginary play	Weight Lifting*	
Listen to music	Wrestling*	**Leisure Activities**
Play indoors with toys		Rollerblading/roller-skating
Playing board games, cards	**Leisure Activities**	Skiing, snowboarding, sledging
Playing computer games (e.g. playstation, gameboy)	Bike riding (not school travel)	Skipping rope
	Bounce on the trampoline	Tag
Playing musical instrument	Bowling	
Reading	Play on playground equipment	
Sitting talking	Scooter	
Talk on the phone	Skateboarding	
Travel by car/bus to school	Walk the dog	
Using computer/Internet	Walk for exercise/hiking	
Watching TV/videos	Horseback riding**	
Cub scouts*	Golf / miniature golf*	
Choir / Singing class*		
Traveling in car to pick up sibling*	**Activities at School and Home**	
Circus skills club/drama club*	Physical education class	
Shopping/walking in mall*	Travel by walking to school	
Texting friends*	Travel by cycling to school	
Church*	Wii Fit**	
Piano lessons*	Marching band*	
	Yoga*	
	Mowing the lawn*	
	Gardening*	
	Farm chores*	

** Activity not on original CPAQ questionnaire, added by investigator; * Added by respondents under "other"

Table 3.2. Characteristics of the sample by Down syndrome status

	DS N=110 Mean (sd)	TD N=29 Mean (sd)	2-sided p-value T-test
Age in years	11.05 (4.25)	12.52 (3.90)	0.095
BMI percentile	72.54 (26.73)	59.16 (31.47)	0.023

	DS %	TD %	2-sided p-value Chi-square test
Gender, Male	75.45	20.69	<0.001
Age group			0.099
5 to 12 years	68.18	51.72	
13 to 18 years	31.82	48.28	
Relation of respondent to child			0.796
Mother	95.45	96.55	
Father	4.55	3.45	
Siblings			0.783
None	13.76	13.79	
Younger sibling(s) only	28.44	37.93	
Older sibling(s) only	35.78	31.03	
Younger and older siblings	22.02	17.24	
Country of residence			
USA	90.00	100.00	0.790
Overweight (BMI $\geq$ 85% & BMI <95%)	20.56	24.14	0.677
Obese (BMI % $\geq$ 95)	26.17	6.9	0.026
Ever had a sleep study	48.18	0	<0.001
Ever diagnosed with Sleep apnea	34.55	0	<0.001
Ever had tonsillectomy	55.45	6.9	<0.001
Ever had heart surgery	22.73	0	0.005
Ever diagnosed with GI disease	21.82	3.45	0.022
Ever used CPAP	15.45	0	0.024
Using CPAP now	6.36	N/A	N/A
Exposure to cigarette smoke			0.205
Not at all	95.45	86.21	
Rarely: 1-2 times a month	2.73	10.34	
Occasionally: 1-2 times a week	0.91	3.45	
A few days a week: 3-4 times	0.91	0	
5-7 days a week	0	0	

DS: Down syndrome; TD: typical development; sd: standard deviation; BMI: body mass index; CPAP: continued positive air pressure; GI: gastrointestinal

Table 3.3. Sleep duration on weeknights, weekends and averaged hours of sleep over one week; SDBS score and % SDBS score ≥5, by age group and DS status

	Ages 5 to 12 years			Ages 13 to 18 years			All ages, 5 to 18 years		
	DS	TD	p-value	DS	TD	p-value	DS	TD	p-value
Sleep variables	n=75	n=15		n=35	n=14		n=110	n=29	
Averaged weekday & weekend hours of sleep	9 h 39 m	9 h 53 m	0.476	9 h 2 m	8 h 8 m	0.011	9 h 28 m	9 h 3 m	0.11
Weekday hours of sleep	9 h 39 m	9 h 47 m	0.672	8 h 58 m	7 h 41 m	<0.001	9 h 26 m	8 h 49 m	0.026
Weekend hours of sleep	9 h 39 m	10 h 5 m	0.250	9 h 17 m	9 h 13 m	0.879	9 h 32 m	9 h 40 m	0.655
SDBS score (mean, sd)	4.16 (1.64)	3.43 (1.16)	0.117	4.66 (1.56)	3.33 (0.89)	0.008	4.32 (1.63)	3.38 (1.02)	0.006
SDBS presence, SDB score ≥ 5	26.47%	14.29%	0.334	46.88%	8.33%	0.018	33%	12%	0.031

Table 3.4. OLS regression results; outcome variable: average nightly hours of sleep; hypothesis 1; (explanatory: continuous SDBS)

N=124	Univariable (individual independent variables, without controlling for other variables)		Multivariable Model 1		Multivariable Model 2	
Explanatory variables	Coefficient (95% CI)	p-value	Coefficient (95% CI)	p-value	Coefficient (95% CI)	p-value
DS	25 (-6 to 57)	0.118	10 (-23 to 43)	0.542	15 (-18 to 48)	0.371
Age in years	-8 (-10 to -5)	<0.001	-8 (-10 to -5)	<0.001	-7 (-10 to -5)	<0.001
Gender, male	1 (-26 to 27)	0.963	5 (-22 to 32)	0.721	11 (-17 to 39)	0.433
SDBS score (continuous)	-7 (-15 to 1)	0.095	--	--	-7 (-15 to 1)	0.073
R^2			0.20		0.23	
F-test for significance of change in R^2 with addition of SDBS score					3.27	0.0733

Table 3.5. OLS regression results; outcome variable: average nightly hours of sleep; hypothesis 1; (explanatory: dichotomous SDBS)

N=124	Univariable (individual independent variables, without controlling for other variables)		Multivariable Model 1		Multivariable Model 2	
Explanatory variables	Coefficient (95% CI)	p-value	Coefficient (95% CI)	p-value	Coefficient (95% CI)	p-value
DS	25 (-6 to 57)	0.118	10 (-23 to 43)	0.542	14 (-18 to 46)	0.394
Age in years	-8 (-10 to -5)	<0.001	-8 (-10 to -5)	<0.001	-7 (-10 to -4)	<0.001
Gender, male	1 (-26 to 27)	0.963	5 (-22 to 32)	0.721	16 (-12 to 43)	0.258
SDBS presence (dichotomous)	-37 (-65 to -10)	0.009	--	--	-38 (-64 to -12)	0.005
R^2			0.20		0.26	
F-test for significance of change in R^2 with addition of SDBS presence					8.30	0.005

Note: Coefficients of regression & 95% CI were multiplied by 60 for reporting as number of minutes.

Table 3.6. Weekly minutes of most common activities, number & percent of parents reporting activity, mean, SD and range for DS and TD groups; and daily minutes of MPVA

	DS (n=104)			TD (n=23)		
Vigorous Activity, MET > 6	n (%)	mean (sd)	Range	n (%)	mean (sd)	Range
Running or jogging	26 (25%)	110 (109)~	10-420	9 (39%)	267 (394)~	20-1200
Basketball/Volleyball	25 (24%)	128 (197)*	20-900	3 (13%)	475 (630)*	60-1200
Tag	25 (24%)	45 (35)	10-160	5 (22%)	66 (44)	20-140
Football/Soccer	16 (15%)	130 (186)**	10-600	3 (13%)	670 (375)**	300-1050
Martial Arts	11 (11%)	136 (88)	45-270	1 (4%)	90	--
Moderate Activity, 3-6 METs						
PE	73 (70%)	109 (81)	20-450	13 (57%)	106 (72)	30-300
playground~	59 (57%)~	148 (124)	15-600	8 (35%)	205 (120)	30-420
Dancing	45 (43%)	164 (255)	10-1500	7 (30%)	184 (172)	45-480
Walk or hike	33 (32%)	87 (116)	15-600	7 (30%)	108 (58)	45-210
Trampoline	30 (29%)	83 (126)	5-600	4 (17%)	98 (110)	15-255
Bicycling	25 (24%)	92 (101)	10-480	4 (17%)	65 (33)	20-90
Swimming lessons~	24 (23%)~	57 (44)	15-180	2 (9%)~	33 (4)	30-35
Swimming for fun~	21 (20%)~	208 (292)	10-960	1 (4%)~	60	--
WiiFit	22 (21%)~	137 (103)	30-420	1 (4%)~	45	--
Walk the dog	17 (16%)	55 (36)	15-140	5 (22%)	66 (42)	30-130
Bowling	16 (15%)*	113 (53)	45-240	0	--	--
Aerobics	12 (12%)	97 (80)	25-300	2 (9%)*	225 (106)	150-300
Gymnastics	12 (12%)	68 (42)*	30-180	5 (22%)	318 (381)*	45-960
horseback riding	8 (8%)*	63 (20)	40-95	0	--	--
Walk to school	6 (6%)**	68 (30)	30-100	6 (26%)**	76 (23)	50-103
Light Activity, < 3 METs						
TV*	98 (94%)	600 (418)**	60-2160	21 (91%)	333 (230)**	60-1080
Car bus to school	87 (84%)	213 (179)	10-840	18 (78%)	110 (88)	20-300
reading	82 (79%)	227 (293)	30-2400	17 (74%)	303 (313)	90-1140
play indoors	77 (74%)**	472 (439)	60-2400	9 (39%)	389 (196)	130-660
listen to music	74 (71%)	397 (440)	30-2280	14 (61%)	510 (376)	60-1260
imaginary play	71 (68%)	355 (268)	30-1320	9 (39%)	475 (403)	78-1080
household chores	67 (64%)	91 (87)	15-420	18 (78%)	103 (90)	2-420
Computer Internet	63 (61%)	384 (375)	60-2280	16 (70%)	449 (356)	30-1140
Homework	58 (56%)**	202 (271)**	10-1800	21 (91%)	470 (478)**	60-1920
Arts	56 (54%)	192 (269)	15-1800	15 (65%)	163 (170)	30-540
computer games	42 (40%)	294 (256)	15-1110	7 (30%)	189 (146)	40-420
play with pets	40 (38%)	101 (110)	15-600	8 (35%)	60 (32)	20-120
board games	33 (32%)	145 (204)	30-1140	7 (30%)	135 (90)	45-240
Sit talk on phone	27 (26%)	348 (588)	15-2640	10 (43%)	500 (688)	25-2100
Play house	19 (18%)	242 (267)	30-1080	2 (9%)	40 (7)	35-45
All LA	104 (100%)	2552 (1258)	420-6976	23 (100%)	2421 (1733)	120-5905
All MPA	104 (100%)	461 (336)	30-1670	21 (91%)	451 (346)	30-1490
All VPA**	69 (66%)	163 (174)*	10-900	16 (70%)	406 (417)*	20-1200
All MVPA	104 (100%)	569 (370)	30-1670	23 (100%)	694 (533)	30-1810
Daily min. of MVPA	104 (100%)	81 (53)	4-239	23 (100%)	99 (76)	4-259

** Significantly different between DS & TD, p-value<0.01, *p-value<0.05, ~p-value >0.05 & <0.10

Table 3.7. Logistic regression results; odds ratio (OR), 95% confidence interval (CI); Outcome: obesity (BMI ≥ 95th percentile); hypothesis 3.

N=124	Univariable (individual independent variables, without controlling for other variables)		Multivariable Model 1		Multivariable Model 2	
Explanatory variables	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value
DS	4.79 (1.07-21.44)	0.041	3.24 (0.64-16.30)	0.154	2.55 (0.48-13.50)	0.271
Age in years	0.91 (0.82-1.00)	0.060	0.91 (0.82-1.01)	0.082	0.93 (0.83-1.04)	0.202
Gender, male	2.16 (0.85-5.47)	0.106	1.65 (0.59-4.62)	0.340	1.86 (0.63-5.46)	0.260
Weekly hours of MVPA	0.87 (0.79-0.96)	0.005	--	--	0.87 (0.78-0.96)	0.006
Pseudo R^2			0.07		0.13	
χ^2 for significance of change in pseudo R^2 with addition of MVPA hours					7.41	0.007

Table 3.8. Logistic regression results; OR, 95% CI; Outcome: presence of SDBS (SDBS score ≥ 5); hypothesis 4.

N=124	Univariable (individual independent variables, without controlling for other variables)		Multivariable Model 1		Multivariable Model 2	
Explanatory variables	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value
DS	3.78 (1.06-13.49)	0.041	1.18 (0.25-5.52)	0.831	0.63 (0.12-3.40)	0.591
Age in years	1.06(0.97-1.17)	0.184	1.06 (0.95-1.17)	0.283	1.12 (0.99-1.25)	0.065
Gender, male	4.96 (1.77-13.92)	0.002	3.50 (1.11-11.02)	0.033	3.48 (1.00-12.13)	0.050
Ever had heart surgery	1.81 (0.70-4.66)	0.219	1.46 (0.51-4.15)	0.480	1.83 (0.59-5.62)	0.292
Ever had tonsillectomy	3.74 (1.64-8.56)	0.002	2.90 (1.16-7.29)	0.023	4.80 (1.65-13.96)	0.004
Obesity (BMI ≥ 95th percentile)	3.90 (1.59-9.55)	0.003	--	--	5.78 (1.90-17.61)	0.002
Pseudo R^2			0.13		0.22	
χ^2 for significance of change in pseudo R^2 with addition of obesity					9.54	0.002

Appendix 3.A.

Analyses relating to meeting 60 minutes of daily recommended MVPA

Logistic regression models

Univariable models Outcome: meeting recommended MVPA (dichotomous variable)			Multivariable model Outcome: meeting recommended MVPA	
Explanatory variables	OR (95% CI)	p-value	OR (95% CI)	p-value
DS presence	0.82 (0.32-2.11)	0.679	0.44 (0.13-1.48)	0.187
Age in years	1.04 (0.96-1.14)	0.328	1.06 (0.95-1.19)	0.307
Gender, male	1.34 (0.64-2.83)	0.439	1.20 (0.48-3.02)	0.701
SDBS score	1.03 (0.81-1.31)	0.804	0.97 (0.74-1.28)	0.845
hours of night sleep	1.12 (0.84-1.51)	0.439	1.39 (0.93-2.07)	0.104
Ever had heart surgery	0.93 (0.38-2.27)	0.871	1.14 (0.40-3.24)	0.809
Ever had tonsillectomy	2.09 (1.00-4.36)	0.051	2.72 (1.12-0.60)	0.028

Ordinary least squares multivariable regression model
Outcome: minutes of daily MVPA (continuous variable)

Explanatory variables	Coefficient (95% CI)	p-value
DS presence	-29 (-62 to 5)	0.094
Age in years	2 (-2 to 5)	0.323
Gender, male	6 (-20 to 32)	0.662
SDBS score	-5 (-13 to 2)	0.156
hours of night sleep	1 (-9 to 11)	0.864
Ever had heart surgery	7 (-22 to 35)	0.656
Ever had tonsillectomy	24 (-1 to 48)	0.060

Appendix 3.B.

1. Results of four multivariable OLS regression models. Outcome: SDB symptoms score; Hypothesis 2a
VPA model N=84; other models N=124-127

	Explanatory variables	Coefficient (95% CI)	p-value
Model for Light Activity	DS presence	0.7 (0 to -0.08)	0.077
	Age in years	0.04 (0 to -0.03)	0.274
	Gender, male	0.51 (0 to -0.15)	0.129
	Weekly hours of LA	0 (0 to 0)	0.848
Model for Moderate Activity	DS presence	0.62 (0 to -0.19)	0.133
	Age in years	0.04 (0 to -0.03)	0.258
	Gender, male	0.47 (0 to -0.19)	0.16
	Weekly hours of MPA	0 (0 to -0.01)	0.261
Model for Vigorous Activity	DS presence	0.43 (0 to -0.76)	0.472
	Age in years	0.06 (0 to -0.04)	0.224
	Gender, male	0.55 (0 to -0.46)	0.284
	Weekly hours of VPA	0 (0 to -0.02)	0.585
Model for Moderate / Vigorous Activity	DS presence	0.58 (0 to -0.21)	0.148
	Age in years	0.04 (0 to -0.03)	0.253
	Gender, male	0.53 (0 to -0.13)	0.114
	Weekly hours of MVPA	0 (0 to -0.01)	0.326

2. Results of four multivariable OLS regression models. Outcome: Nightly hours of sleep*; Hypothesis 2b
VPA model N=84; other models N=124-127

	Explanatory variables	Coefficient (95% CI)	p-value
Model for Light Activity	DS presence	14 (-19 to 48)	0.398
	Age in years	-8 (-10 to -5)	<0.001
	Gender, male	4 (-23 to 32)	0.754
	Weekly hours of LA	0 (0 to 0)	0.144
Model for Moderate Activity	DS presence	10 (-26 to 46)	0.587
	Age in years	-8 (-11 to -5)	<0.001
	Gender, male	7 (-22 to 35)	0.643
	Weekly hours of MPA	0 (0 to 0)	0.332
Model for Vigorous Activity	DS presence	-1 (-55 to 52)	0.959
	Age in years	-8 (-12 to -4)	<0.001
	Gender, male	5 (-38 to 49)	0.804
	Weekly hours of VPA	0 (-1 to 0)	0.333
Model for Moderate / Vigorous Activity	DS presence	14 (-21 to 50)	0.42
	Age in years	-8 (-11 to -5)	<0.001
	Gender, male	6 (-22 to 34)	0.659
	Weekly hours of MVPA	0 (0 to 0)	0.682

* Coefficients & CI were multiplied by 60 to report number of minutes

Chapter 4

Conclusions, Practice Implications, and Direction for Future Research

Conclusions, practice implications, and direction for future research

The presence of Down syndrome in all human populations, regardless of race, ethnicity or social standing, has been stable worldwide, with a slight increase in live birth rates in the United States over the past few decades. Increases in survival and life expectancy (1, 2) warrant a holistic approach to health and prevention or decrease of modifiable health risks in this population. Sleep disordered breathing (SDB) is prevalent in many children with Down syndrome, but its presence is not inevitable.

The studies within this dissertation demonstrated that SDB symptoms adversely affect the successful accomplishment of daily life habits, and that SDB is strongly associated with obesity in children with DS. These studies have contributed new knowledge to the field of sleep in Down syndrome. The findings strongly support the idea that within children with DS, who are already at a disadvantage in accomplishing life's daily tasks, compared to children with typical development (TD), improved sleep has the capacity to increase the success of daily life activities. Moreover, within the same sample, it was demonstrated that SDB is strongly associated with overweight and obesity. Obesity is a modifiable risk factor, not only for SDB, but for many other adverse health outcomes (3, 4) . Also within this same sample, it was demonstrated that more physical activity (PA) was positively associated with less obesity. It is important that these relationships were all observed within one sample of children, because the effect of known and unknown confounding factors is diminished when different phenomena are studied in one and the same sample population.

The inclusion of a comparison sample of children with TD demonstrated that all children, regardless of DS status, have the same patterns in the relationship of SDB with sleep duration and obesity, although these patterns may be more pronounced in DS. Beside surgical and clinical intervention, finding successful behavioral preventive interventions, to help children with DS overcome or reduce the modifiable risk factors of SDB, can help all children; as interventions that work in a most affected population also usually successfully help the general population.

Future research in sleep and PA patterns of children with DS is warranted. The present studies used subjective measures and yet demonstrated relationships in 3 of 5 hypothesized scenarios. Precise, accurate and objective measurement can strengthen these findings. For example, parent-reported height and weight likely underestimate overweight and obesity. Clinically measured obesity, and biomarkers of inflammatory response in obesity, would confirm and strengthen these findings. Demonstration of hypotheses about the direct relationship of PA with SDB and sleep duration can benefit from objectively measured PA intensity and timing.

The present studies provide justification for designing and implementing behavioral interventions that work hand-in-hand with clinical and surgical interventions to curb SDB in children with DS. It is noted importantly, that surgical intervention alone, for example tonsillectomy, is not always adequate to resolve SDB completely. Tonsillectomy is important for reducing if not eliminating SDB symptoms, and based on the findings of these studies may ease the performance of PA for children with DS. Enhanced performance of PA in turn could curb obesity and SDB.

Looking beyond the present studies, SDB may have far-reaching effects in other aspects of health which need to be investigated within DS populations with implications for the general population. For example, Alzheimer’s disease (AD) is prevalent in adults with DS (5, 6). SDB has been implicated in AD (7), and a clinical trial in adults has shown that treatment of SDB can have positive effects on cognitive function is patients with AD (8). What would the implications be in DS? In DS, even with a genetic disposition to AD, it has been suggested that nonpharmacological cognitive intervention may curb AD (9). With treatment and prevention of SDB in children with DS, if cognitive and behavioral function is improved, then could it be that the pathway of AD could be altered? These questions need exploration, not only to improve the outcomes of children and adults with DS, but because lessons learned for AD in Down syndrome are far-reaching for the general population as well (5). While there have been many genetic studies about the role of the DS genotype in development of AD, further studies are needed for translating the knowledge into preventive or curative clinical and behavioral strategies, given that plausible mechanisms for curbing AD (5), SDB and obesity exist.

Of especial interest is intervention to curb obesity in DS, given obesity is implicated in many health outcomes including SDB. Rates of childhood obesity had been on the increase in the United States for the past few decades, but since 2007 there has been stabilization in the rate of childhood obesity (10). This stabilization is an improvement over increasing rates but improvements are needed in actual reduction of obesity in all children. Likely children with DS follow the general trends in obesity as other children; however, the standard of measuring obesity in children with DS is different and less stringent than obesity standards of children with TD. The United States DS childhood obesity standards are based on historical growth curves of children with DS in one US state in the 1970s and 1980s (11). New standards, in line with standards of obesity in children with TD, are needed. The present study used the obesity standard of children with TD and found a greater proportion of children with DS overweight or obese than children with TD. One reason some previous studies of SDB in DS had not found obesity as a risk factor for SDB may have been the use of historical DS growth charts (12).

Intervention to reduce obesity in DS will not be an easy feat, just as in the TD population, and likely even more challenging than in the TD population. Reduction in overweight and obesity in DS has to become a long-term generational goal, accepted and promoted by the health care system and families. It is important to create more opportunities for increased PA in safe environments for children with DS and other disabilities, not only for weight control but for the many other benefits that PA affords. However, while increased PA and reduction in obesity will likely have effects in reduction in the symptoms of SDB in the future, continual monitoring and assessment of normal- and under-weight children for SDB remains important in the DS population.

While the present studies do not establish absolute causality, several characteristics of these studies lend credibility to them: 1) agreement with scattered studies in non-DS and DS populations, 2) a dose-response relation between obesity and SDB symptoms, 3) a dose-response relation between SDB symptoms and sleep duration, 4) biological plausibility of the discussed mechanisms and their interworkings. Thus, there is hope that SDB and obesity are not inevitable in DS. There exist modifiable risk factors that can be controlled and bent to improve health and life quality.

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Vita

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