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Sleep and sleep disordered breathing in children with Down syndrome: effects on behaviour, neurocognition and the cardiovascular system

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Summary

Down syndrome (DS), the most common human chromosomal malformation, has an estimated annual incidence of 1 in 1,000 live births worldwide. Sleep problems are common in children with DS, reported by parents in up to 65% of school-aged children, significantly higher rates than in typically developing (TD) children. Problems include difficulty in sleep initiation and maintenance together with obstructive sleep apnoea (OSA) which affects up to over 90%, of DS children compared with 1-5% in the general paediatric population. Any sleep problem has the potential to exert significant negative effects on daytime behaviour, learning and quality of life in TD children and there is now a growing body of evidence that children with DS are similarly affected. In addition to adverse effects on daytime functioning, OSA has adverse effects on the cardiovascular system and this is a particularly significant issue given the high rates of hypertension and premature cardiac disease in people with DS.. This review discusses the effects of sleep problems and OSA on daytime functioning and cardiovascular function in children with DS and evidence of the effectiveness of treatment in improving outcomes and quality of life for these children.

Key words: sleep, daytime behaviour, quality of life, cardiovascular, Down syndrome, paediatric

Abbreviations:

ABAS, adaptive behaviour assessment system

ACTB, Arizona cognitive test battery

AHI, apnoea hypopnoea index

AT, adenotonsillectomy

BRIEF, behaviour rating inventory of executive function

CBCL, child behaviour checklist

CHD, congenital heart disease

CPAP, continuous positive airway pressure

CSHQ, children's sleep habits questionnaire

DABS, diagnostic adaptive behaviour scale

DS, Down syndrome

GAC, general adaptive composite

HR, heart rate

HRV, heart rate variability

IQ, intelligence quotient

Life-H, life habits questionnaire

MCDI, MacArthur communicative development inventory

MLST, multiple sleep latency test

MRI, magnetic resonance imaging

MSEL, Mullen scales of early learning

NREM, non-rapid eye movement

OAHI, obstructive apnoea hypopnoea index

OSA, obstructive sleep apnoea

PAP, positive airway pressure

PS, primary snoring

PSG, polysomnography

PSQ, paediatric sleep questionnaire

REM, rapid eye movement

RPM, Raven progressive matrices

SDB, sleep disordered breathing

SDQ, strengths and difficulties questionnaire

SE, sleep efficiency

SOL, sleep onset latency

SpO_2, peripheral oxygen saturation

TD, typically developing

TST, total sleep time

WASO, wake after sleep onset

WISC, Wechsler intelligence scale for children

Introduction

Down syndrome (DS), or Trisomy 21, so-named because people with DS have an extra chromosome 21, is the most common human chromosomal disorder, with an annual incidence of 1 in 650-1000 births annually worldwide [1-3]. The rate of live births of children with DS decreased significantly with the introduction of prenatal screening and access to medical termination of pregnancy in the 1980s, but has remained relatively constant over the last 20-30 years [4]. The vast majority of cases of DS are attributable to errors in oogenesis during the first maternal meiotic division, and advanced maternal age at conception is the highest risk factor for having an infant with DS [5, 6]. Although it is known that DS occurs at conception, to date, why it occurs remains unknown. DS occurs across ethnicities and irrespective of social strata, however, disease prevalence varies among countries due to differing sociocultural and economic factors [7]. DS is the most common inherited form of learning disability, and in developed countries accounts for 12-15% of those with learning disabilities [8]. Better care and medical treatment have led to an increase in average life expectancy of a person with DS in developed countries from 35 years in 1982 to approximately 60 years in 2002 [9, 10]. Optimising the health of children with DS to optimise quality of life, and identifying problems that could lead to secondary complications as early as possible are of the utmost importance.

Sleep has a significant impact on quality of life, daytime functioning [11] and the cardiovascular system [12]. While children with DS may have a number of different factors that impact on their cognitive and cardiovascular outcome, this review will focus on the effect of sleep disruptions and in particular sleep disordered breathing (SDB).

Physical dysmorphologies in children with Down syndrome

The dysmorphic features that characterise people with DS include small ears, brachycephaly, flat face, epicanthic folds, flat nasal bridge, small mouth with protruding large tongue, short neck with a bulge of fat at the back, broad hands, Simian fold, sandal gap, hypotonia, and hyperflexibility [7, 13]. Between 44 - 58% of children with DS have a congenital heart defect (CHD), including atrioventricular septal defects (45%), ventricular septal defects (35%), isolated secundum atrial septum defects (8%), isolated persistent patent ductus arteriosus (7%), isolated tetralogy of Fallot (4%) and other lesions (1%) [14].

Distinct dysmorphic features, such as mid-face and mandibular hypoplasia, relatively large and medially positioned tonsils, and macroglossia, result in a significant reduction in the size of the upper airway in people with DS, when compared to normal airways [15, 16]. Additionally, the obesity and generalised hypotonia, which are also common in people with DS, contribute to the collapse of the upper airway during sleep and contribute significantly to respiratory compromise during sleep, and thus SDB [16, 17].

Sleep in children with Down syndrome

Sleep is a major physiological drive that is essential for normal growth and development of both the body and the brain. During childhood, sleep is at a lifetime maximum, with preschool children spending half of each 24 hours asleep and primary school aged children only slightly less. Sleep, particularly the deeper stages of non rapid eye movement (NREM) sleep, plays an important role in learning by promoting the consolidation and integration of memory and has a significant effect on daytime behaviour in typically developing (TD) children [11]. Any disorder which disrupts sleep, such as SDB is of particular importance during childhood, as central nervous system maturation continues during this time and developing areas are likely to be more vulnerable to injury [18]. Recent brain imaging studies have identified that SDB in childhood is accompanied by predominantly acute brain changes

in areas that regulate autonomic, cognitive, and mood functions, and chronic changes in frontal cortices essential for behavioural control [19].

Studies of sleep and sleep problems in children with DS are summarised in Table 1.

The majority of studies have assessed sleep problems in children with DS using parental questionnaire, the most commonly used questionnaire being the Children's Sleep Habits Questionnaire (CSHQ). This measure has been shown to be reliable compared to other measures of sleep, medical history of sleep problems and daily reports of sleep and sleep behaviours in children with DS [20].

Parental reports show that children with DS have an increased prevalence of sleep problems, particularly problems with initiating and maintaining sleep, which can lead to excessive daytime sleepiness, compared to TD children [21-23]. Despite the high incidence of parentally reported sleep problems, the extent of sleep problems are frequently underestimated by parents, with 66% of parents of children with sleep problems identified by validated questionnaires not perceiving their child to have a sleep problem when asked directly [22].

A study of children with DS (N=91) aged 4-19 years compared with their siblings (N=54) and children from the general population (N=78), identified that sleep problems were significantly greater in the children with DS compared with both their siblings and the general population [24]. Sleep problems included difficulty settling at bedtime (20% of children with DS), night wakening (32%), reluctance to go to bed (26%), co-sleeping with parents or siblings (9%), enuresis (16%), sleep talking (19%), bruxism (17%), head banging (7%), and sleepwalking (3%) [24]. A similar study of 58 children with DS (0.65-17.9 years of age) compared sleep habits using the CSHQ with published data from TD children. The study reported that the children with DS had significantly greater bedtime resistance, sleep anxiety,

night waking, parasomnias, SDB and day-time sleepiness [25]. Furthermore, 66% rarely fell asleep in their own beds, 55% were always restless during sleep, 40% usually woke at least once during the night, and 78% seemed tired during the day at least 2 days per week, suggesting insufficient good quality sleep. As part of a larger study of sleep in children with intellectual disabilities, parental descriptions of sleep problems in children with DS (N=15; aged 2-18 years) was compared with that of TD children (N=55) [26]. The parents answered a questionnaire using a 100mm visual analogue scale to rate the severity of the sleep problem for their child. Sleep problems included sleep behaviour, daytime napping, excessive daytime sleepiness, settling habits, bedtime routines, and night waking. The parents of children with DS reported significantly more problems with sleep maintenance compared with the TD children, and 33% had more than one reported sleep problem. However, with only 15 children with DS, this is a very small study and therefore difficult to generalise to the wider DS population.

In a large online survey of 110 children with DS and 29 TD children aged 5 to 18 years, parents competed the CSHQ and the life habits questionnaire [23]. Sleep disturbance was negatively associated with accomplishment of daily activities. In particular, an increase in SDB score was associated with 10 of the 11 life habits questionnaire domains, which were responsibility, community life, personal care, education, recreation, mobility, mealtimes, fitness, relationships and home life. Although sleep duration was longer in the 13-18 year old children with DS compared to the TD children, daytime sleepiness score was higher in the children with DS [23]. The authors suggested that treating sleep disturbance could improve deficits in several life habits by over 20% [23]. In a cross-sectional study of children with DS which examined the caregiver-reported sleep behaviours of 108 children with DS, ranging in age from 1.50 to 13.40 years (mean = 5.18 years) 76% of children with DS were reported to have sleep problems, which began at a young age, and continued to persist and recur with

increasing age [27]. In a study of 34 children aged 9-15 years and a matched control group of TD children, children with DS were reported by parents to have significantly higher scores on the CSHQ, including increased bedtime resistance, sleep anxiety, night waking, SDB and daytime sleepiness, with the most common behavioural problem being attention-deficit/hyperactivity [28]. DS children exhibited lower scores on the diagnostic adaptive behaviour scale than the TD children. Both IQ and the total sleep disturbance score were significant predictors of attention-deficit/hyperactivity scores and both IQ and attention-deficit/hyperactivity scores were predictive of adaptive skills [28]. Parent reported sleep problems assessed as a composite score of problems reported on the CSHQ were related to temperament assessed with the Early Childhood Behaviour Questionnaire when compared between 19 children with DS and 20 TD children aged 18 months to 4 years [29]. Consistent with previous studies, the children with DS exhibited more sleep problems. In addition, temperament between the groups also differed, with children with DS exhibiting less effortful control (temperament related to the self-regulation of emotional reactivity and behaviour) than TD children [29]. The authors suggested that sleep problems may serve as both a cause and a consequence of the difference in temperament between the groups.

In summary, parental reports show that sleep problems are very common in children with DS and even though sleep problems are more common than in TD children they tend to be under-reported. Furthermore, parental reports of sleep problems have been associated with behavioural problems, quality of life and temperament in some studies.

Fewer studies have used objective measures of sleep quality such as actigraphy to investigate sleep and sleep problems in children with DS. Using 7 days of actigraphy a cross sectional study of 66 infants and young children with DS aged 5-67 months showed that the developmental trajectories of circadian rhythms were similar to those of TD children, despite increased sleep fragmentation and lower sleep efficiency [30]. Sleep efficiency, as measured

by 1 week of actigraphy in 30 children with DS aged 6-17 years, was not related to either parental or teacher reports of behaviour assessed by the Nisonger Child Behaviour Rating Form and the Vanderbilt ADHD Rating Scales, however parent reports of restless sleep assessed by the CSHQ were [31]. In the same group of children, again actigraphic measures of sleep were not related to executive functioning, as assessed by the Behavior Rating Inventory of Executive Function (BRIEF), but parental reports of restless sleep were predictive of parental concerns with inhibitory control, shifting and working memory and of teacher reports of inhibitory control [32]. In a study which compared a clinically referred group of children, who wore an actigraph during one night of polysomnography, with a group of children recruited from the community who wore an actigraphy for 1 week at home, the authors concluded that actigraphy demonstrated convergent validity with polysomnography when measuring total sleep time, total wake time after sleep onset and sleep efficiency in children with DS and again demonstrated a poor correlation with parent reports of sleep [33]. Studies in TD children have shown that actigraphy is reliable for determining total sleep time and sleep efficiency but overestimates wake time compared to polysomnography [34], thus the study highlights the limitations of subjective parental reports of sleep. In another actigraphic study of 29 toddlers with DS and 24 TD toddlers aged 26-64 months, the DS toddlers exhibited increased sleep disturbance with reduced sleep efficiency [35]. The toddlers were subsequently divided into poor sleepers and good sleepers based on sleep efficiency, with a sleep efficiency <80% defining poor sleep. 66% of the toddlers with DS exhibited poor sleep compared to only 15% of the TD toddlers. Poor sleep was related to greater deficits on parental reports of language, including vocabulary and syntax [35].

Using objective measures of sleep/wake patterns with actigraphy and measures of oxyhaemoglobin saturation with overnight pulse oximetry, children with DS (N=22) aged 6-13 years had increased night awakenings and fragmented sleep, lower peripheral oxygen

saturation (SpO_2), increased SpO_2 dips and increased SpO_2 variability, suggestive of SDB compared to TD children (N=41) [36]. Children with DS had impaired attention, however this was not predicted by sleep disruption or SpO_2 and the authors suggested that other confounding factors such as environmental aspects, motivation or other characteristics of the syndrome may also have contributed [36].

Polysomnographic studies are considered the gold standard for assessing sleep and sleep disruption. Polysomnographic studies have identified that adults with DS have less rapid eye movement (REM) sleep and it was speculated that this may have implications for learning and memory [37]. Early polysomnographic studies which compared children with DS (N=10) to TD children with primary snoring (PS) (N=13) did not identify any differences in median length of epochs of slow wave or REM sleep, but children with DS had shorter epochs of N2 sleep [38]. Similarly, a study comparing 32 children with DS aged 3.5-8.2 years with TD children, matched for age and SDB severity, found the children with DS spent significantly more time in N1 sleep but there were no differences in the other sleep stages or sleep efficiency [39]. A more recent polysomnographic study in a larger group (N=130) of children with DS aged 2-17 years reported that sleep efficiency was lower, the percentage of N3 sleep higher, and the percentage of REM sleep lower in those 7-11 years compared with age, gender and BMI matched TD children. There were no differences in sleep architecture in those children under 2 years of age [40]. In another study of children with DS (N=45) aged 1-16 years who were studied before adenotonsillectomy (median apnoea hypopnoea index (AHI) 10.1 events/h) had less REM and N1 sleep compared to normative data for non snoring control children [41]. Children younger than 6 years had more N2 and N3 sleep but those older than 6 years had similar amounts compared to the control group [41]. After surgery, the differences in sleep architecture remained, despite a decreased in AHI.

In summary, sleep problems particularly disorders of initiation and maintenance of sleep in young children and excessive daytime sleepiness in older children are more common in children with DS than in TD children. The majority of studies have used parental report of sleep and sleep disturbances. Parental report is subjective and often biased [42], however in children with DS, parental reports tend to underestimate sleep problems. There have been fewer studies using objective measures of sleep such as actigraphy and polysomnography. These studies also show more sleep disruption in children with DS compared to TD children and have also identified associations with behaviour, quality of life and temperament. Differences in sleep architecture have been reported, but are hard to interpret given frequent poor quantification of the contribution of SDB to the abnormalities seen.

Sleep disordered breathing (SDB) in children with Down syndrome

Sleep presents a major challenge to the respiratory system compared with wakefulness, due to fundamental physiological differences in respiratory mechanics and control [43]. Consequently, any impairment of breathing will be more significant during sleep compared with wakefulness. In children, enlarged tonsils and adenoids in relation to the size of the bony structure of the airway are the primary cause of sleep-related breathing disorders [44]. Obstructive SDB is a common condition in TD children, with prevalence estimates ranging from 4 to 11% [45]. SDB is a continuum of severity ranging from primary snoring (PS) to obstructive sleep apnoea (OSA). At the mild end of the spectrum, children with PS do not exhibit sleep fragmentation or gas exchange abnormalities. At the severe end of the spectrum, OSA is characterised by repeated episodes of complete or partial upper airway obstruction with resultant hypoxia, hypercapnia and sleep disturbance. OSA occurs in 1% to 5% of TD children [46]. TD children with SDB experience adverse health effects including behavioural and neuropsychological impairment [47] and an increased risk of adverse cardiovascular

outcomes, including elevated heart rate and blood pressure, and decreased control of both heart rate and blood pressure and in severe cases, cardiac remodelling [48].

The incidence of SDB is far higher in children with DS, where the condition affects 31-97%, depending on the patient selection criteria, definitions and methodology used [49-58]. The increased incidence of SDB in children with DS is contributed to by many physical and functional factors that increase susceptibility to SDB. In particular, the atypical anatomical airway structure, which includes a small oropharynx, narrow upper airway structure with medially positioned tonsils and relative tonsillar and adenoidal encroachment, mid-facial hypoplasia, mandibular hypoplasia and an enlarged tongue, predispose children with DS to SDB [59-61]. Moreover, children with DS have decreased muscle tone, which further limits the flow of air and restricts optimal respiration [62]. An increased incidence of upper respiratory tract infections contributing to enlargement of the tonsils and adenoids [46], obesity [63, 64], and hypothyroidism associated with reduced respiratory drive [65], also increase the risk of SDB.

In a recent study of over 200 children with DS aged 6 months to 6 years, moderate to severe OSA, defined as an obstructive apnoea hypopnoea index (OAHI) of > 5 events/h was found in 14% and mild OSA, defined as an OAHI of ≥ 1 and ≤ 5 events /h, was found in 59% of children [57]. In a study which recruited over half of all children born with DS in Norway in 2002, 28/29 had an apnoea hypopnoea index >1.5 event/h and 24/29 had an obstructive apnoea index >1 event/h, 66% were diagnosed with moderate to severe OSA [56]. The prevalence of OSA has been reported to be higher in boys (64.7%) compared to girls (38.5%) and in younger children [55]. One study of children aged 0.3-16.9 years found more severe OSA in children with DS (n=98) referred for investigation of suspected SDB compared to referred TD children (n=278) [54], which the authors suggested reflected a relative reluctance

by parents or doctors to investigate symptoms of SDB in children with DS. The extent of symptoms was not different however between the groups for a given severity of SDB [17].

Screening for SDB in children with DS

Because of the increased prevalence of SDB in children with DS, the American Academy of Pediatrics recommend that all children with DS have an overnight polysomnographic study by the age of 4 years, as significant OSA may be present in these children despite the lack of indication on history or physical examination [66]. However, polysomnography is difficult to access in many countries, and may be poorly tolerated in young children, particularly those with intellectual disability. Moreover, research has not specifically addressed the prevalence of the condition in asymptomatic children, or identified the peak prevalence by age, noting that SDB has been described from infancy in DS [50]. A recent study of children with DS aged 6 months to 6 years identified that severity of OSA was not predicted by age, tonsillar size or BMI and recommended that all pre-school children be screened for OSA with objective measures of OSA severity [57]. The study provides evidence that home based cardiorespiratory polygraphy is acceptable to most families and provides an alternative approach to in laboratory polysomnography. A more recent study by the same group found that a measure of baseline SpO_2 variability on home oximetry provided a 92% sensitivity for identifying children with moderate-severe OSA [67]. As highlighted above, children with DS commonly also have behavioural sleep disturbances that co-exist and may mask the presence of SDB, making it difficult for both parents and physicians to determine the best timing of assessment of OSA severity.

A retrospective study of 954 children with DS aged 5-21 years, found only 47.7% of these children has undergone polysomnography, 39.1% had diagnosed sleep problems, of which

81.2% had received sleep intervention according to the diagnosis of the sleep problem [68]. Sedating medication was the most common sleep treatment for children with behavioural sleep disturbances with no diagnosis of OSA, followed by behavioural interventions. Surgery was the most common treatment for children with OSA or OSA and behavioural sleep disturbances, followed by positive airway pressure (PAP). The children with DS and comorbid OSA were more likely to be obese, which is a risk factor for OSA in TD children as well as children with DS. The reason that over half of the children had not had polysomnography may be multifactorial, reflecting both the level of physician concern and barriers to polysomnography, including parental reluctance to have their child complete a study that may require hospitalisation, and lack of access to a paediatric sleep specialist with competency working with this population of children [68, 69]. Alternatives to in-hospital polysomnography, such as home-based cardiorespiratory polygraphy and new diagnostic screening tools, are being developed and assessed however further research is required to determine their utility in surgical decision-making in this population [69].

Effect of sleep disordered breathing on behaviour and neurocognition in children with Down syndrome

Children with DS have some degree of intellectual disability, and commonly exhibit behavioural and neurocognitive impairment, particularly hyperactivity, lack of attention, impaired memory, and decreased school performance [28, 31]. There is growing evidence to suggest that the presence of SDB may contribute to the delay in behaviour and cognitive performance in these children. Studies of the effect of SDB on behaviour and neurocognition in children with DS are summarised in Table 2.

In a non-referred community based sample of children with DS aged 7-12 years, those who had comorbid OSA (N=12), defined as an AHI >1.5 events/h, scored 9 points lower on verbal IQ assessed with the Arizona Cognitive Test battery compared with those who did not have OSA (N=19) [27]. Full scale and Non-verbal IQ did not differ between the groups. Executive function tasks and performance measures on cognitive flexibility were completed less well in those children with OSA. This study highlights that OSA may contribute to the neurodevelopmental deficits of DS. . In contrast, another small study of 25 children aged 7-19 years, found no difference in cognitive function between those who did not have OSA defined as an AHI< 1.5 events/h (N=19), and those with OSA (N=10) defined as an AHI>5 events/h [70]. Cognitive function was related to total sleep time and sleepiness as measured by the multiple sleep latency test, and adaptive functioning and achievement were predicted primarily by the time spent in N3 sleep [70]. Interestingly, there were no differences in parental report of snoring, witnessed apnoea, or daytime somnolence between those children with and without OSA [70]. A study of preschool children with (N=22) and without DS (N=22) used home sleep cardiorespiratory polygraphy and divided children into high and low AHI groups (which had a higher cut off for the DS compared to the TD group) [71]. In the TD children, longer sleep duration was associated with higher scores for expressive language and fewer emotional symptoms, and in these children SDB was associated with increased conduct problems and less prosocial behaviour. In contrast, although the children in the DS group exhibited lower scores on all objective and parental reports of cognition and behaviour than the TD group, SDB was associated with increased language understanding and the use of actions and gestures [71]. The authors suggested that this finding was due to multiple factors that masked the association between SDB and behaviour and cognition in the DS children.

In 29 older adolescents and young adults aged 14-31 years, parental rating of OSA severity did not relate to other sleep problems, but was associated with poor verbal fluency and inhibition [72]. The authors suggested that the development of the prefrontal cortex is negatively affected by OSA in the DS population as it is in the TD population [72]. A study that examined the effects of SDB severity on adaptive functioning in 30 children with DS with a median age of 9.1 years found an association between SDB severity and communication skills.

In summary, there have been limited studies on the effects of SDB on behaviour and daytime functioning in children with DS. There is evidence that SDB is negatively associated with cognition in children with DS as it is in TD children. The numbers of children included in most studies have been small and all the studies to date have been cross-sectional. In addition, not all have shown a relationship between SDB severity and outcome measures. Thus, more research is required to clarify the relationship between SDB and neurocognition in children with DS, and to identify if treatment of SDB is associated with improvements in outcomes. As the life expectancy of patients with DS increases there are additional complications which occur with aging. One such complication is Alzheimer's Disease, which is more prevalent in the DS population [73]. OSA is associated with disruption to sleep architecture, intermittent hypoxia, oxidative stress, intrathoracic and haemodynamic changes, as well as cardiovascular comorbidities. All of these could increase the risk for Alzheimer's Disease [74], thus OSA is a potential modifiable target for Alzheimer's Disease prevention.

Effect of sleep disordered breathing on cardiovascular functioning in children with Down syndrome

In addition to neurocognitive and behavioural sequelae, in TD children SDB is associated with a significant effect on the cardiovascular system, with studies reporting increased sympathetic activity, elevated blood pressure and heart rate, together with reduced autonomic control of both blood pressure and heart rate [48]. Children with DS who also have SDB are therefore likely to exhibit similar or more severe cardiovascular dysfunction [75]. Studies investigating the effect of SDB on the cardiovascular system in children with DS are presented in Table 3.

Cardiovascular and pulmonary diseases account for approximately 75% of the mortality in DS patients [76]. Congenital heart disease (CHD) is frequently diagnosed in DS patients and up to 54% of infants with DS are born with CHD [77, 78]. However, there has been a reduction of 2% per annum in the number of infants with DS born with complex CHD since 1992, which is attributed to increased rates of termination of pregnancy following earlier detection by echocardiography of fetuses with complex CHD [78]. The most common forms of cardiac problems seen in patients with DS include complete atrial-ventricular canal, ventriculospetal defect and atrioseptal defect [79]. These underlying cardiovascular and pulmonary diseases may be exacerbated by comorbid SDB in children with DS.

Older studies proposed OSA as a mechanism for pulmonary hypertension in children with DS, and suggested that *cor pulmonale* occurred secondary to OSA in children with hypertrophy of the adenoids and tonsils [80, 81], which could be reversed by relieving the upper airway obstruction [82, 83]. A recent study of children with DS aged 8-19 years without unrepaired congenital heart disease, in which 20 out of the 23 participants had OSA (AHI 5.3-80.6 events/h) reported that while left ventricular diastolic function was associated with OSA severity, no pulmonary hypertension was detected by echocardiography [84]. The authors postulated that their results could be due to the benefits of improvements to the management of DS, such as earlier cardiac surgery. However, all of the children but one in the study had

undergone previous adenotonsillectomy, thus possibly resulting in a shorter duration of OSA for the children during a period of critical development than in the earlier studies.

During wakefulness, studies have identified that adults and children with DS exhibit attenuated heart rate and blood pressure responses to autonomic challenges, such as exercise and orthostatic challenges [85-88]. However, these studies did not account for the participants' possible SDB status, which could potentially worsen the cardiovascular response to these challenges. In addition to exercise and orthostatic challenges, arousal from sleep also activates a cardiorespiratory response. In healthy individuals, arousal triggers large transient increases in heart rate and blood pressure, which are associated with acute sympathetic activation and parasympathetic withdrawal [89]. Similar studies in children with DS are scant. In one study of children aged 3-17 years, 10 children with DS and OSA (OAHI >1 event/h), 10 TD children with OSA matched for age and OSA severity, and a further 10 non-snoring TD control children, underwent overnight polysomnography [90]. The heart rate response to arousal from sleep was examined by analysing beat-by-beat heart rate from 15s before a spontaneous arousal to 15s post arousal. While arousals were associated with significant increases in heart rate in all of the groups, the heart rate response in children with DS and OSA was significantly lower compared with the TD children with or without OSA. Whether this attenuated cardiovascular response to arousal was due to reduced sympathetic activity or blunted vagal withdrawal could not be ascertained. However, these findings could have implications for the cardiovascular impact of OSA in children with DS.

At the termination of respiratory events, TD children with SDB have a surge in both heart rate and blood pressure with accompanying hypoxia and arousal, which are believed to cause an increase in sympathetic tone in children with SDB [91, 92]. . A study of 32 children with DS and SDB (2-17 years), and 32 TD control children matched for age and SDB severity, analysed the change in heart rate beat-by-beat over the course of obstructive respiratory

events [39]. The children with DS had a significantly reduced heart rate response following respiratory events compared with the control group. Overnight urinary catecholamines were also analysed in this study as an indication of sympathetic activity in the body as a whole. Children with DS and SDB had significantly reduced overnight urinary noradrenaline, adrenaline and dopamine compared with the TD children with SDB. Both the heart rate response to obstructive events and the reduced urinary catecholamines indicate a dampened sympathetic response to SDB in children with DS. The authors concluded that the combination of a compromised acute cardiorespiratory response, coupled with a dampened sympathetic response to SDB, may reflect autonomic dysfunction in children with both DS and SDB, placing them at an increased risk of cardiovascular complications, including pulmonary hypertension [39].

Heart rate variability (HRV) is a non-invasive measure of autonomic control of the heart. HRV measures the beat-by-beat changes in heart rate from the R-R intervals on the electrocardiogram. Power spectral analysis of the R-R intervals separates HRV into low frequency power, reflecting both sympathetic and parasympathetic activity, high frequency power, reflecting parasympathetic activity and the ratio of low to high frequency power, which is an indication of sympathovagal balance. Several studies have demonstrated that HRV is altered in an age dependent manner in TD children with SDB (for review see [48]). The majority of studies that investigated HRV in individuals with DS have done so in the context of recovery from or during isometric or dynamic exercise during wakefulness and in adult populations, without regard for SDB status. These studies are beyond the scope of this review, however one study has shown that children with DS, even without CHD or respiratory disorders exhibit autonomic dysfunction, indicated by increased low frequency and decreased high frequency power compared with TD controls [93]. To our knowledge there has been only one study that has assessed HRV in children with DS and SDB. A small

study of 7 children with DS and SDB aged 8.6-16.5 years and 6 control children (8.0-17.5 years) with no neurological, otorhinolaryngological or cardiovascular abnormalities, reported increased low frequency power (reflecting both sympathetic and parasympathetic activity) and decreased high frequency power (reflecting parasympathetic activity) in the children with DS and SDB compared with the controls [94].

In summary, there have been limited studies of the effects of SDB on the cardiovascular system in children with DS, however these all suggest a dampened autonomic response to SDB compared to TD children and highlight the need for more research to investigate the additive effects of DS and SDB on the cardiovascular health in these particularly vulnerable children.

Effect of treatment for sleep disordered breathing in children with Down syndrome

Adenotonsillectomy (AT) is the most common treatment for OSA in TD children. AT is effective in most cases but there is a sub-set of children who have residual OSA following AT, especially children who are obese. A randomised control trial of early AT (surgery within 4 weeks of randomisation) versus watchful waiting, in TD children with mild OSA reported normalisation of OSA in 79% of the early AT group compared with 46% of the watchful waiting group [95]. Normalisation of OSA was reduced in obese children to 67% of the early AT group and 29% of the watchful waiting group. A retrospective study of 578 children aged 18 months to 18 years, compared pre and post AT polysomnography data and reported that while there was a significant reduction in AHI, only 27.2% had complete resolution of OSA (AHI<1 event/h) [96]. Age and body mass index (BMI) Z-score were the factors that principally contributed to the post AT AHI. However, although complete cure is not always achieved, with the significant improvements in OSA severity following AT, it

remains the most common first-line treatment option for OSA in children. Other treatment options for SDB in children include continuous positive airway pressure (CPAP) therapy, topical corticosteroids, leukotriene receptor antagonists, and dental/orthodontic treatments (for review see [97]).

SDB in children with DS is often more complex than in TD children and other additional treatment options, such as CPAP, in addition to AT may be required [98]. Studies of the effectiveness of treatment for SDB in children with DS demonstrate a significantly reduced chance of cure following AT compared to TD children, with 73% of children with DS in one study requiring CPAP, bi-level PAP or supplementary oxygen for persistent OSA after AT [99]. Similar findings have been reported in numerous other studies (for review see [100]) and highlight the need for post-surgical follow-up in these children. None-the-less, a systematic review of the literature addressing AT in treating OSA in children with DS, concluded that a 51% reduction in the preoperative AHI could be expected with AT alone [90].

A magnetic resonance imaging (MRI) study found that there are multiple causes of persistent OSA following surgery in children with DS, including macroglossia (large tongue), glossoptosis (downward displacement or retraction of the tongue), recurrent enlargement of the adenoid tonsils and enlarged lingual tonsils [62]. Identification of these anatomical structures that cause the persistence of OSA in children with DS, would be helpful in determining the need for further surgical procedures and also for identifying which procedures would be optimal for cure. Successfully employed treatment options for residual OSA in children with DS include tracheostomy, mandibular distraction osteogenesis for children with significant retrognathia, genioglossus advancement, rapid maxillary advancement, lingual tonsillectomy, tongue reduction, tongue hyoid advancement or

suspension, uvulopalatopharyngoplasty, tonsillar pillar plication, and laryngotracheoplasty [101] and recently hypoglossal nerve stimulation [102].

Studies in TD children with SDB have identified that even small improvements in SDB severity can improve cardiovascular [103, 104], quality of life and behavioural outcomes [95], therefore an improvement in SDB severity could also be expected to result in improved outcomes in children with DS. However, to date there is only scant research investigating the effect of treatment on the neurocognitive and behavioural sequelae of SDB in children with DS in the literature. Six children with DS were included in a sub-sample of ten children with neurodevelopmental disability in a study that analysed the effect of PAP therapy on neurobehavioural outcomes in a heterogeneous group of 52 children aged 2-16 years with OSA [105]. Following three months of PAP use, the children with developmental delay had significant improvements in daytime sleepiness, internalising and total behaviour scores, and quality of life. The authors noted however, that the study was underpowered for the developmentally delayed children and changes in other behavioural parameters may have been missed.

Quality of life is an important measure of clinical outcome following OSA treatment. A study of 80 children with either DS or mucopolysaccharidosis and comorbid OSA aged 6-12 years, assessed AHI, the Epworth sleepiness scale–child and adolescent and the OSA-18 as a measure of quality of life, before and 6 and 12 months following treatment [106]. The children were randomly assigned to receive either coblation AT or CPAP. In the AT group, 37 children completed the study with 36 completing the study in the CPAP group. Both groups of children had similar and significant improvements in OSA severity measured by the AHI, and in daytime sleepiness measured by the Epworth sleepiness scale–child and adolescent. The timing of the improvement over the 12 months of the study differentiated the groups, with the children receiving CPAP showing an immediate and sustained improvement

and the children who had AT showing a more gradual and progressive improvement. Significant improvements in quality of life following both treatments were also found, indicated by improvements in the total OSA-18 score, particularly the domains of sleep disturbance, physical suffering and daytime problems. However, as the authors noted, evaluation of the outcomes of treatment for OSA is complex in syndromic children, as neither surgery nor CPAP address the other comorbidities that affect them. The major limitation of this study was that the number of children with each syndrome was not provided, and presuming that children with DS have different underlying comorbid conditions than children with mucopolysaccharidosis, determination of the specific effect of treatment on quality of life in children with DS cannot be made.

Another study investigated whether OSA was worse in adults with DS who were obese compared with age, gender and BMI matched non-DS adults [107]. As hypothesised, the adults with DS had more severe OSA than the non-syndromic participants. As an adjunct to the study, the authors reported on 9 of the subjects with DS who were referred for treatment and who were followed-up in the same sleep centre following an undisclosed period of time on CPAP. Of these 9 patients, family members of the five who had excellent use of CPAP (6-8 h/night) reported the DS patients had an improvement in daytime functioning. However, these were informal responses to questioning by sleep centre staff and not by any scientific measure.

Studies of the effects of treatment of OSA on cardiovascular outcomes in children with DS are even more limited. In one study, 20 children with DS and comorbid OSA (OAHI ≥5 events/h) aged 8-19 years who had previous AT were randomised to either a therapeutic CPAP or a sham CPAP group following baseline polysomnography [84]. Both groups were given a month of habituation and intensive behavioural therapy by a paediatric behavioural psychologist, followed by a CPAP titration polysomnography study. The children on sham

CPAP also had a mock titration study where no pressure changes were made. A final polysomnographic study was conducted following 3 months of CPAP treatment. Cardiovascular assessments conducted at baseline and at 4 months included: awake blood pressure and plasma brain natriuretic peptide levels (a peptide continuously secreted by the heart to regulate blood pressure and fluid balance in response to ventricle volume expansion and pressure overload). In addition, echocardiography measured left ventricular mass, the thickness of the interventricular septum, the thickness of the left ventricular posterior wall, and a measure of left ventricular diastolic function. Despite the intensive behavioural therapy provided to participants, CPAP adherence was suboptimal (median CPAP use at pressure was116 (range 70-139) min/night at month 4). There were no significant changes in cardiovascular parameters between the children randomised to actual versus sham CPAP at four months. However, unexpectedly the duration of actual CPAP use was inversely associated with the change in left ventricular diastolic function, and was positively associated with left ventricular mass. If CPAP adherence had been better, an improvement in cardiovascular outcomes may have been identified, however these results need to be verified with a larger cohort.

In summary, there is evidence from TD children that treatment of OSA improves cardiovascular and daytime outcomes, however there have been very few studies in children with DS and this is an area which requires significantly more research.

Conclusions

Children with DS have an increased prevalence of sleep problems, including difficulties in initiating and maintaining sleep and excessive daytime sleepiness, compared to TD children. Additionally, the craniofacial abnormalities, obesity and hypotonia that characterise the

condition significantly increase their risk of SDB, further adding to their sleep disturbance. Despite recommendations for early diagnosis and treatment, less than half of the children with DS undergo polysomnography to diagnose the severity of SDB. Evidence to date suggests that the presence of SDB may contribute to behaviour and cognitive problems in these children. Furthermore, children with DS and comorbid SDB have attenuated cardiovascular responses to spontaneous arousals and respiratory events, and a dampened sympathetic response, which may exacerbate the adverse cardiovascular effects of this disorder.

The most common treatment for OSA in children with or without DS is AT. Children with DS and comorbid OSA demonstrate a significantly reduced chance of cure following AT compared to TD children, and commonly many children go on to have further treatment such as CPAP. Although the literature is currently limited, children with DS do appear to have less sleepiness, improved quality of life and improved behaviour following AT and/or CPAP. To date, improvements to the cardiovascular sequelae of SDB in children with DS have not been reported.

This review has clearly identified that there are a dearth of studies regarding the threshold for treatment of SDB in children with DS and the effectiveness of treatment of SDB in improving neurocognitive, behavioural and cardiovascular outcomes in children with DS. We highlight that these areas require further research to better inform screening and treatment guidelines for children with DS.

Practice Points

In children with Down syndrome:

1. sleep disorders are more common than in typically developing children;

2. sleep disordered breathing is very common and should be screened for with polysomnography or with home overnight oximetry in the pre-school years;

3. the consequences of sleep disruption and sleep disordered breathing on behaviour, neurocognition, quality of life and the cardiovascular system should be considered when assessing these children.

Research Agenda

In the future we need more research in children with Down syndrome to:

1. identify the effectiveness of treatment of sleep disorders, particularly sleep disordered breathing, in improving daytime functioning and cardiovascular control;

2. establish the threshold of severity of sleep disordered breathing warranting treatment;

3. establish the prevalence and severity of sleep disordered breathing in asymptomatic children to inform the need for screening children without symptoms

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Table 1. **Sleep in children with Down syndrome**

Citations	**Design**	**Sample/Studies**	**Outcome/Conclusion**
Ashworth et al. (2015) [36]	Prospective	DS children aged 6-12 y (n=22) and TD children aged 6-12 y (n=41); actigraphy.	DS children had poorer SE, shorter SOL, higher number of night awakings and increased fragmentation index relative to TD children .
Carter et al. (2009) [25]	Prospective	DS children aged 0.65-17 y (n=58) compared with published data from TD children; CSHQ.	DS children more likely to experience bedtime resistance, Sleep onset delay, sleep anxiety, night awakenings, SDB (45% snoring and 2% with apnoea and daytime
Churchill et al. (2014) [23]	Prospective	Parents of DS children aged 5-18 y (n=110) and age matched TD children (n=29); CSHQ.	Significantly higher scores of sleep problems in DS children in age groups. Significantly higher reports of night awakenings, and SDB in DS children.

Cotton & (2006) [26]	Retrospective	DS children aged 2-18 y (n=15) and TD children (n=55); non-validated sleep questionnaire.	DS children had more sleep maintenance problems and 33.3% had more than one type of sleep problem.
Diomedi et al. (1999) [37]	Prospective	DS subjects aged 17-31 y (n=8) and TD subjects aged 13-20 y (n=8); PSG.	Significantly less REM sleep, higher number of night time awakenings and lower SE in DS cohort.
Edgin et al. (2015) [35]	Prospective	DS children (n=29) and TD (n=24) aged 26-64 months; actigraphy and CSHQ.	Significantly lower SE, higher WASO and poorer fragmentation index in DS children. DS were more likely to present with SDB.
Esbensen et al. (2018) [31, 32]	Prospective	DS children aged 6-17 y (n=30); sleep diary, actigraphy, BRIEF.	Parent reported parasomnias and restless sleep correlated with more daytime behavioural issues. Sleep period and SE correlated with the parent reported executive functioning.
Esbensen et al. (2018) [33]	Prospective	DS children aged 6-17 y (recruited from clinic n=27; community n=47);	DS children with OSA on both PSG and actigraphy had in the time in bed, TST and total number of wake episodes

		PSG, actigraphy, CSHQ.	compared to DS children without OSA. Using the SHQ subscale, 84.4% of DS children exhibited sleep problems, 34% reported of bed resistance and 20% of all children had poor SE.
Fernandez et al. (2017) [30]	Prospective	DS children (n=66) and TD (n=53) aged 5-67 months; actigraphy.	SE and TST significantly poorer in DS children.
Hoffmire et al. (2014) [22]	Prospective	Parents of DS children aged 7-17y (n=107) population-based cohort; CSHQ and PSQ.	Sleep problems reported in 65% using CSHQ and 46% using PSQ. 21% had sleep related movement disorders. and . 46% SDB had on the PSQ.
Kelmanson (2017) [28]	Prospective	DS children aged 9-15 y (n=34) and age and sex matched TD children (n=34); CSHQ.	Significantly higher bedtime resistance, sleep anxiety, night waking, daytime sleepiness and total disturbance score in DS children.
Levanon et al. (1999) [38]	Prospective	DS children aged 1-8 y (n=23) and TD children aged 2-7 y(n=13);	No differences in TST, SE or REM sleep in DS group. DS

		PSG, parental sleep questionnaire.	had significantly less N2 sleep.
Lukowski et al. (2017) [29]	Prospective	DS children aged 18-53 months (n=19) and aged matched TD children (n=20); CSHQ.	More sleep problems reported in DS children. DS cohort had less TST and were significantly more likely to snore loudly. They asleep within 20 minutes of going to bed. DS children more to seem tired during the daytime..
Mims et al. (2017) [41]	Retrospective	DS children aged 1-16 y (n=45) compared to normative data for non-snoring children; PSG.	Time spent in REM and N1 sleep significantly lower in DS children. In the DS children < 6 y, mean time spent in N2 was significantly higher whereas in the DS children >6 years mean time in N3 was higher.
Nisbet et al. (2015) [40]	Retrospective	DS children aged 0-18 y (n=130) and aged matched TD children (n=30); PSG.	Significantly higher AHI and lower SE in DS children aged >2 y. No differences in sleep architecture in children < 2 years. % N3 sleep higher in DS children >2 years, whilst all DS children a less % N2 sleep. Significantly lower TST in the older DS

Table 2. **Studies relating sleep disruption to behaviour, neurocognition and quality of life in children with Down syndrome and comorbid sleep disordered breathing.**

Citations	Design	Sample/Studies	Outcome/Conclusion
O'Driscoll et al.]	Prospective	DS children aged 2-17 years (n=32) (n=32); PSG	DS children spent significantly less TST in N1. No significant children. N1 we
Rosen et al. (2011) [21]	Prospective	Parents of DS children aged <1-<18 years, median 5 years; (n=255); internet based questionnaire.	Difficulties initiating sleep in 51.8% and difficulties maintaining sleep in 69.4% of children.

AHI, apnoea hypopnea index; BRIEF, behaviour rating inventory of executive function; CSHQ, childhood sleep habits questionnaire; DS, Down syndrome; OSA, obstructive sleep apnoea; PSG, polysomnography; PSQ, pediatric sleep questionnaire; REM, rapid eye movement sleep; SDB, sleep disordered breathing; SE, sleep efficiency; SOL, sleep onset latency; TD, typically developing; TST, total sleep time; WASO, wake after sleep onset.

Breslin et al. (2014) [27]	Prospective	DS children aged 7-12 y (n=38); with and without OSA. PSG, CSHQ and ACTB.	Verbal IQ 9 points lower in the DS OSA children. Executive function poorer in the DS OSA children.
Brooks et al. (2015) [70]	Prospective	DS children aged 7-18 y with OSA (n=10) and without OSA (n=19); PSG, MLST, neuropsychological tests.	No difference in cognitive or neuropsychological functioning between children with or without OSA. Cognitive functioning correlated with TST, sleepiness. Adaptive behaviour and achievement associated with time spent in N3.
Chen et al. (2013) [72]	Prospective	DS adolescents and young adults aged 14-31 y (n=29); sleep questionnaire and cognitive function tests.	Verbal fluency negatively correlated with parental ratings of OSA severity.

Churchill et al. (2015) [23]	Prospective	DS children aged 5-18 y (n=110) and TD children (n=9); CSHQ and Life-H data.	Significant association between SDB severity and lower scores in 10 out of 11 Life-H data. Daytime sleepiness score higher in DS children.
Joyce & Dimitriou (2017) [71]	Prospective	DS children aged 24-56 months (n=22) and TD children aged 25-59 months (n=22); home sleep cardiorespiratory polygraphy, MSEL, SDQ and MCDI.	Children with DS scored worse on all scales of cognition and behaviour. No correlation between SDB and behaviour or cognition in DS children. DS children a higher understanding of actions and gestures compared to TD children and these were correlated with SDB.
Nixon et al. (2016) [17]	Prospective	DS children (n=30) comprised of primary snorers (n=5), mild OSA	Difficulties in adaptive functioning with increasing

Table 3. **Studies investigating cardiovascular sequelae in children with Down syndrome and comorbid sleep disordered breathing.**

Citations	**Design**	**Sample/Studies**	**Outcome/Conclusion**
Ferri et al. (1998) [94]	Prospective	DS children aged 8-16 y (n=7) and TD children aged 8-17 y	Children with DS had increased LF and decreased HF compared to TD children during N2. No marked changes in HRV evident during other

(n=7) and moderate to severe severity of OSA 30% had a GAC OSA (n=18); ABAS. score lower than average. 77% scored in the extremely low range and 89% presenting with moderate to severe OSA fell in this extremely low range.

ABAS, adaptive behaviour assessment system; ACTB, Arizona cognitive test battery; CBCL, child behaviour checklist; CSHQ, childhood sleep habits questionnaire; DABS, diagnostic adaptive behaviour scale; DS, Down syndrome; GAC, general adaptive composite; Life-H, life habits questionnaire; MCDI, MacArthur communicative development inventory; MLST, multiple sleep latency test; MSEL, Mullen scales of early learning; OSA, obstructive sleep apnoea; PSG, polysomnography; RPM, Raven progressive matrices; SDB, sleep disordered breathing; SDQ, strengths and difficulties questionnaire; WISC, Wechsler intelligence scale for children.

		(n=6); PSG, HRV.	sleep stages or REM sleep.
Konstatinopoulou et al. [84] (2016)	Prospective	DS children aged 8-19 y (n=23); PSG, brain natriuretic peptide and echocardiography.	None of the participants demonstrated pulmonary hypertension however worse left ventricular diastolic functioning was correlated with increasing OSA severity.
O'Driscoll et al. (2010) [90]	Retrospective	DS children aged 3-17 y (n=10), age-matched TD children with OSA (n=10), and without OSA aged 7-12 ys (n=10); PSG; HR response to arousals.	The heart rate response to arousal was lower in the DS children compared to both the TD + OSA and TD children.
O'Driscoll et al. (2012) [39]	Prospective	DS children aged 3-8 y (n=32) and aged-matched TD children (n=32); PSG, HR response to respiratory events; urine catecholamines.	HR response at respiratory event termination lower in DS children in NREM sleep. Concentrations of urinary noradrenaline, adrenaline and dopamine significantly lower in DS children reflecting an attenuation in sympathetic activation.

DS, Down syndrome; HR, heart rate; HRV, heart rate variability; HF high frequency; LF low frequency; PSG, polysomnography; OSA, obstructive sleep apnoea; TD, typically developing.