



Key points

- Adults with Down syndrome are predisposed to obstructive sleep apnoea/hypopnoea syndrome (OSAHS) due to overlap between the Down syndrome phenotype and OSAHS risk factors.
- The prevalence of OSAHS in adults with Down syndrome is estimated at 35–42%. This is up to ten-times higher than in the general adult population.
- Symptoms of OSAHS, including behavioural and emotional disturbances as well as standard symptoms such as sleepiness, should be monitored as part of regular health surveillance in adults with Down syndrome.
- There is evidence that the use of continuous positive airway pressure (CPAP) therapy in adults with Down syndrome and comorbid OSAHS can lead to significant improvements in subjective sleepiness, behaviour and cognitive function, though further large-scale trials are required.

Educational aims

- To discuss the relationship between the phenotypic features of Down syndrome and the risk factors for obstructive sleep apnoea/hypopnoea syndrome (OSAHS).
- To examine the prevalence of OSAHS in adults with Down syndrome.
- To review recent research into the effectiveness of treatment of OSAHS in adults with Down syndrome using continuous positive airway pressure (CPAP) therapy.



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Obstructive sleep apnoea/hypopnoea syndrome in adults with Down syndrome

Obstructive sleep apnoea/hypopnoea syndrome (OSAHS) is characterised by repeated cycles of upper airway obstruction during sleep, leading to diurnal symptoms. Individuals with Down syndrome are predisposed to OSAHS due to overlap between the Down syndrome phenotype and OSAHS risk factors. Recent large studies using subjective and objective measures estimate that OSAHS affects around 40% of adults with Down syndrome, in contrast to 2–4% of the general adult population. The “double-hit” of comorbid Down syndrome and OSAHS may accelerate cognitive decline in adults with Down syndrome. However, with the appropriate care and support, OSAHS can be treated effectively in this group using continuous positive airway pressure (CPAP) therapy, improving daytime function and behaviour. Symptoms of OSAHS should be routinely monitored in this population, with testing and treatment available to all adults with Down syndrome; however, this is not currently commonplace, and health inequalities are evident.



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Obstructive sleep apnoea/hypopnoea syndrome affects ~40% of adults with Down syndrome but can be treated effectively <http://ow.ly/Jdco3062xP5>

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Introduction

Down syndrome is a common genetic disorder of human chromosome 21 (HSA21), affecting 1 in 1000 live births worldwide [1]. The presence of an additional full or partial copy of HSA21 results in a number of typical features which affect all individuals with Down syndrome, including craniofacial abnormalities and intellectual disability, though there is a wide spectrum of phenotypic expression. Life expectancy continues to rise, now averaging around 60 years, with some individuals living well beyond this. It is estimated that there are over 47000 people with Down syndrome living in the United Kingdom alone [2].

Down syndrome is the most commonly recognised cause of intellectual disability worldwide.

All individuals with the condition have intellectual disability, typically associated with an IQ <70 [3, 4]. These deficits are related to structural and functional changes within the brain, some present from birth and others, such as plaques and tangles associated with dementia, acquired over time [5–7]. The hippocampus, prefrontal cortex and cerebellum are particularly affected, and abnormalities in these regions are related to the cognitive deficits observed in individuals with Down syndrome, including impaired motor function, delayed speech and language, learning and memory problems, and behavioural and emotional disturbances [5, 6, 8].

Obesity is common, affecting up to three-quarters of adults with Down syndrome [9–11]. This is, in part, related to short stature, though



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the cause is multifactorial. Premature ageing is a characteristic feature of Down syndrome, and, as well as features of accelerated ageing *per se*, there is often an earlier onset of other disorders associated with advancing age in the general population, such as hypothyroidism and sensory impairment and, in women, menopause. Virtually all individuals with Down syndrome have neuropathological markers of dementia by the age of 40, accompanied by a decline in cognitive function with age [12]. Congenital heart defects are common and are usually corrected in childhood, though untreated heart defects persist in around 15% of adults with Down syndrome [10].

Despite the range of comorbid health conditions known to be associated with Down syndrome, health inequality exists, and individuals with Down syndrome may not receive the health surveillance and treatment that they require [13, 14]. Diagnostic overshadowing [15] means that common, treatable conditions may be overlooked or left untreated on the basis that they are considered to be “just part of Down syndrome”. However, it is clear that with the correct support, screening and intervention, the majority of individuals with Down syndrome can lead a long and fulfilling life.

Obstructive sleep apnoea/hypopnoea syndrome (OSAHS) is a disorder characterised by repetitive cycles of airway obstruction, resulting in pauses in breathing, sleep fragmentation and intermittent hypoxia, which can in turn lead to diurnal symptoms such as sleepiness, mood impairment and a decline in cognitive function. OSAHS is a common disorder, generally accepted to affect 2–4% of adults in the general population [16]; a more recent follow-up study has reported an increased prevalence of 10–17% in men and 3–9% in women, though this has yet to be replicated [17].

The pathophysiological basis of the disorder is a loss of airway patency. Airway patency is maintained by the action of the pharyngeal dilator muscles and longitudinal traction related to lung volume counteracting the negative pressure generated during inspiration [18]. Factors leading to an increase in airway narrowing and obstruction in the general population include advancing age, male gender, raised body mass index (BMI) and use of sedative drugs, including alcohol [19, 20]. Anatomical and physiological factors which impact on the size of the upper airway, such as obesity, adenotonsillar hypertrophy, craniofacial abnormalities, hypotonia, rapid eye movement (REM) sleep and the effect of gravity in the supine position, also increase the risk. There is a strong hereditary component [21].

Untreated OSAHS impacts adversely on overall morbidity and mortality, and is associated with increased cardiovascular risk, metabolic dysfunction and neurocognitive impairment [22–25]. However, a simple, noninvasive and cost-effective treatment, continuous positive airway pressure (CPAP) therapy, is almost universally available and has been

Table 1 Anatomical and physiological features predisposing adults with Down syndrome to obstructive sleep apnoea/hypopnoea syndrome (OSAHS)

Features predisposing adults with Down syndrome to OSAHS

Obesity/pre-obesity
Midface hypoplasia
Thick neck
Gothic palate
Adenotonsillar hypertrophy
Relative macroglossia
Hypotonia
Increased mucosal secretions

demonstrated to reduce or normalise most of the deleterious effects of untreated OSAHS [26–29].

Comorbid Down syndrome and OSAHS

It is apparent that many of the phenotypic features of Down syndrome overlap with the risk factors for OSAHS, as summarised in table 1. The characteristic craniofacial phenotype of individuals with Down syndrome, with midface hypoplasia and brachycephaly, results in an anatomically reduced pharyngeal space. Generalised hypotonia increases the risk of airway collapse and is compounded by other factors including a thick neck, obesity, relative macroglossia, adenotonsillar hypertrophy and increased mucosal secretions. Being overweight or obese is the most important risk factor for OSAHS. It is likely that the premature ageing evident in individuals with Down syndrome exacerbates the age-related increase in OSAHS risk seen in the general population.

In addition, it is likely that untreated OSAHS has a negative impact on many of the common comorbidities associated with Down syndrome. It has long been recognised that untreated OSAHS leads to cognitive impairment, and, given that adults with Down syndrome are already cognitively impaired by virtue of their intellectual disability, the impact of OSAHS in this population may be even more pronounced. Typically-developing individuals with a high IQ exhibit some resilience to the cognitive effects of untreated OSAHS, due to an increased cognitive reserve, while those in the normal IQ range do not [30]. Therefore, it is likely that those with Down syndrome who have an IQ below the normal range will be even more susceptible to the cognitive impact of OSAHS due to their reduced reserve. There is growing evidence of a causal link between OSAHS and dementia in the

general population [31], and, in adults with Down syndrome, early-onset Alzheimer's-type dementia is almost universal by the age of 40 years [12]. There appears to be overlap between the brain regions which are structurally and functionally affected by Down syndrome and those which are impaired by OSAHS in the general population, particularly the hippocampus, prefrontal cortex and cerebellum [5, 32]. Both disorders impair learning, memory, attention, executive function and motor skills.

Overall, the combination of intellectual disability, early-onset dementia and untreated OSAHS may leave adults with Down syndrome extremely vulnerable to cognitive impairment. FERNANDEZ and EDGIN [33] hypothesised that this "double-hit" may accelerate the age-associated cognitive decline in adults with Down syndrome. It is possible that CPAP therapy may slow age-related cognitive decline in adults with Down syndrome and OSAHS by alleviating sleep fragmentation and intermittent hypoxia. While there are no formal studies in the Down syndrome population, CPAP has been shown to reduce sleep fragmentation and increase the percentage of slow wave sleep in typically-developing adults with mild to moderate Alzheimer's disease and OSAHS [34]. However, it remains to be elucidated how much of the cognitive dysfunction seen in adults with Down syndrome may be related to untreated OSAHS rather than Down syndrome *per se*, how the two disorders interact and how much function can be retained or recovered by diagnosis and treatment of underlying OSAHS in this population.

Untreated OSAHS is related to behavioural and emotional disturbances in children and adults with Down syndrome [35, 36], and depression is common in both individuals with Down syndrome and in adults with OSAHS in the general population. A survey of 28 adolescents and young adults with Down syndrome, who were diagnosed with major depression by a mental health clinic for people with Down syndrome, found that 86% had OSAHS when tested by polysomnography, in comparison with 44% of nondepressed controls. Moderate to severe OSAHS was evident in 54% of cases and 11% of controls [37].

Prevalence of OSAHS in Down syndrome

Despite the clear areas of overlap between the two conditions, very few studies have assessed the prevalence of OSAHS in adults with Down syndrome, and, to date, only three of these studies have used polysomnography, the reference standard tool for diagnosis of OSAHS. In a study conducted in Italy [38], six adults with Down syndrome (three male, three female) aged 28–53 years and from a single residential care facility underwent inpatient polysomnography after an acclimatisation night.

Using a diagnostic apnoea–hypopnoea index (AHI) threshold value of $\geq 10 \cdot h^{-1}$, five of the six participants (83%) had obstructive sleep apnoea (OSA), symptoms of OSAHS not being assessed. A second study included 16 adults with Down syndrome aged 19–56 years and recruited from a Down syndrome specific clinic and Down syndrome advocacy groups in the United States [39]. Using an AHI cut-off of $>15 \cdot h^{-1}$, all but two of the participants (88%) had OSAHS. One further study recruited 12 young adults with Down syndrome from a day centre in Greece and conducted polysomnography in the participants' own homes [40]. All 12 participants demonstrated an AHI value of $>10 \cdot h^{-1}$, though daytime sleepiness (as assessed using the Epworth Sleepiness Scale) was within the normal range in all cases. However, all three studies are limited by the very small number of participants and factors such as ethnicity, obesity and residential status mean that the results may not be indicative of the wider population of adults with Down syndrome as a whole.

These studies suggest that the prevalence of OSAHS in the Down syndrome population is greatly elevated; however, small participant numbers and methodological issues underline the need for larger, population-based studies. A recent population-based survey of over 1100 adults with Down syndrome aged ≥ 16 years and living in the United Kingdom estimated a prevalence of 35%, based on self-reported symptoms (Hill *et al.*, personal communication). Subsequent objective measurement in a subset of this cohort, *via* level III unattended home polygraphy ($n=134$), demonstrated a diagnosis of OSAHS in 42%, using an AHI cut-off value of $\geq 10 \cdot h^{-1}$ in symptomatic participants. Home polygraphy was generally well-accepted, with a reportable study obtained after one or two nights' consecutive recording in the majority of cases.

Treatment of OSAHS in Down syndrome

Given that the likely prevalence of OSAHS in adults with Down syndrome reported in the literature is so high, it is perhaps surprising that very little evidence relating to efficacy or acceptability of CPAP therapy exists.

Trois *et al.* [39] reported anecdotally on the outcome of CPAP therapy in eight adults with Down syndrome identified as having OSAHS. Seven individuals underwent CPAP titration with fixed-pressure CPAP, while another commenced bilevel ventilation. Five of the eight adults on treatment had an excellent compliance of 6–8 h per night, with their families reporting a subjective improvement in sleepiness and daytime function. However, no formal subjective or objective measures of CPAP efficacy were made.

More recently, a prospective trial of CPAP therapy [41] was undertaken in a cohort of 28

Self-evaluation questions

- Adults with Down syndrome are at risk of obstructive sleep apnoea/hypopnoea syndrome (OSAHS) due to:
 - Relative macroglossia.
 - Midface hypoplasia.
 - A tendency to be overweight or obese.
 - All of the above.
- The prevalence of OSAHS in adults with Down syndrome is:
 - Currently unknown.
 - No different to that of the general population.
 - Estimated at 35–42% using subjective and objective measures.
 - Estimated at 10–17% using subjective and objective measures.
- Which of the following is not true regarding continuous positive airway pressure (CPAP) therapy in adults with Down syndrome and OSAHS?
 - CPAP is contraindicated in adults with Down syndrome and OSAHS.
 - No published studies have formally assessed the effectiveness of CPAP in this patient group.
 - Unpublished pilot data suggest that CPAP can improve sleepiness, behaviour and cognitive function in adults with Down syndrome and OSAHS.
 - A large-scale randomised, controlled trial of CPAP in adults with Down syndrome is yet to be realised.

adults with Down syndrome identified as having OSAHS during the UK prevalence study discussed above (Hill *et al.*, personal communication). Participants were young adults (mean age 28±9 years) with moderate to severe intellectual disability, 74% of whom were overweight or obese. Participants were initiated on CPAP therapy by an experienced CPAP nurse with follow-up over a 12 month period. A battery of cognitive function tests and standard measures of sleepiness and behavioural/emotional dysfunction were administered at baseline and during the follow-up visits. At 1 month, CPAP usage was low at 2.8 (1.1–6.7) hours per night. By 12 months, no significant difference in CPAP compliance was noted. However, this first prospective study of CPAP therapy in adults with Down syndrome demonstrated that, despite small participant numbers, even modest use leads to sustained, significant improvements in subjective sleepiness, measures of disruptive and depressive behaviour, and cognitive function in the verbal domain over a 12-month period. Of the 28 participants enrolled in the study, four had

withdrawn by 12 months and a further five opted not to continue beyond the end of the trial period. However, CPAP therapy appears to be effective and well-tolerated in this population, with over two-thirds of individuals continuing to use it beyond the end of the trial. Reasons for quitting CPAP were diverse, relating to both patient and parental concerns, and CPAP side-effects were similar to those noted in the general population. Given the potential benefits in terms of improved daytime function and quality of life, a further, larger-scale randomised, controlled trial in this population is warranted.

Discussion

Despite a clearly increased risk of OSAHS in adults with Down syndrome and significant overlap between the deleterious consequences of both disorders, studies of prevalence of OSAHS in adults with Down syndrome and the benefits of treatment in this population are scarce. Screening for OSAHS should form a standard component of ongoing health surveillance in adults with Down syndrome, though large-scale studies of the effectiveness of CPAP therapy in this group are still required. Preliminary data suggest, however, that CPAP therapy can be tolerated by a majority of adults with Down syndrome and that, given the appropriate care and support, OSAHS can be treated effectively, improving daytime function and behaviour.

In a recent study in the United Kingdom (Hill *et al.*, personal communication) only 3% of questionnaire responders had a prior diagnosis of OSAHS despite an estimated prevalence over ten-times higher than this. Further work is required to increase awareness of OSAHS in adults with Down syndrome, highlighting that poor sleep is not “just part of the condition”, but is, in fact, a common comorbidity of Down syndrome affecting more than one in three adults. The increasing life expectancy of individuals with Down syndrome means that the number of adults with this condition living with OSAHS is likely to increase over the coming years. Therefore, testing and treatment should be routinely offered to all adults with Down syndrome, in the same way as in the general population. It is hoped that recent studies and future research will provide vital steps towards this becoming common practice.

Conflict of interest

Disclosures can be found alongside this article at breathe.ersjournals.com

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Suggested answers

- 1 d.
- 2 c.
- 3 a.