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Prevalence and treatment of obstructive sleep apnoea/hypopnoea syndrome in adults with Down syndrome

Elizabeth Anne Hill

Doctor of Philosophy - The University of Edinburgh - 2016

For my family

Declaration

I declare that this thesis has been composed by myself and that the work has not be submitted for any other degree or professional qualification.

I have been the principal investigator in the studies detailed within this thesis, with assistance from colleagues at the Sleep Research Unit at The University of Edinburgh and others, as detailed in the Acknowledgements.

I confirm that the work submitted is my own, with the exception of Chapter 6, which is a collaboration with researchers from Kyushu University, Fukuoka, Japan. My contribution and those of the other researchers to this work have been explicitly detailed within the Acknowledgements and Chapter text.

I confirm that appropriate credit has been given within this thesis where reference has been made to the work of others.

The studies comprising this thesis were conducted at the Department of Sleep Medicine, Royal Infirmary of Edinburgh, or via home visits and domiciliary sleep studies within the United Kingdom, during the period 2011 – 2015.

Elizabeth Anne Hill
October 2016

Abstract of thesis

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 (DS) are predisposed to this as the DS phenotype overlaps with OSAHS risk factors. Around 2-4% of the general adult population and 55% of children with DS have OSAHS but, to date, no large-scale study has assessed OSAHS prevalence or efficacy of treatment in DS adults.

This study aimed to: 1) Systematically assess subjective and objective OSAHS prevalence; 2) Assess the effectiveness of continuous positive airway pressure (CPAP) in an adult DS population.

Standard questionnaires including pictorial Epworth Sleepiness Scale (pESS) and Developmental Behaviour Checklist for Adults (DBC-A) were sent to UK adults aged ≥16yr with DS and their caregivers. All questionnaire responders were invited to undergo home polygraphy. Symptomatic adults with DS with ≥10 apnoeas/hypopnoeas per hour in bed (AH) on home polygraphy were invited to participate in a prospective randomised controlled trial (RCT) of CPAP v. lifestyle advice, with review at 1, 3, 6 and 12m. Participants in the lifestyle arm were offered CPAP at 1m. Standard measurements of sleepiness, behaviour, cognitive function and general health were undertaken. Standard statistical analyses were conducted, with significance set at $p<0.001$ to control for multiple testing.

Of 5270 questionnaires sent, 1105 responses were valid (21%). Responders (55% males) were overweight/obese young adults: mean BMI 29.0±6.8kg/m2; mean age 28±9 years. Women had a higher BMI ($p<0.0001$), but collar size was greater in men ($p<0.0001$). Mean pESS scores were broadly within the normal range (7±5/24). No significant gender differences in OSAHS symptoms were noted. Individuals with probable OSAHS had higher pESS and DBC-A scores, and significantly more symptoms of OSAHS. Subjective OSAHS prevalence was estimated at 35%. Of the 790 individuals invited, 149 underwent polygraphy, with 134 valid studies obtained:

mean AH 21.8(10.9-42.7); mean oximetry desaturation index (ODI) 6.6(2.3-20.0). No significant gender differences were observed. Forty-two percent of participants met standard clinical diagnostic criteria for OSAHS. Twenty-eight eligible adults with DS (19 male) were randomised: age 28±9yr; BMI 31.5±7.9kg/m2; AH 28.6(14.8-47.9); ODI 7.3(1.8-21.9); pESS 11±6/24. Groups did not differ significantly at baseline. By 12m, 4 participants had withdrawn (all remaining participants on CPAP). The pESS ($p=0.001$), DBC-A Disruptive ($p<0.0001$) and Kaufmann Brief Intelligence Test verbal subscale ($p=0.001$) scores improved significantly.

This first large study of OSAHS prevalence in the adult DS population estimates a prevalence of 35-42% - around 10 times higher than in the general adult population. Sustained, significant improvements in sleepiness, cognitive function and behavioural/emotional outcomes with CPAP use over a 12m period were demonstrated during this first RCT of CPAP in adults with DS. A larger trial of CPAP in this population is warranted.

Lay summary of thesis

Obstructive sleep apnoea/hypopnoea syndrome (OSAHS) is a condition in which repeated breathing pauses during sleep cause daytime symptoms such as sleepiness. People with Down syndrome (DS) are prone to this as some of the features of DS are also risk factors for OSAHS. We think that 2-4% of the general adult population and 55% of children with DS have OSAHS but, to date, no large studies have looked at how many adults with DS have OSAHS or how well treatment works for them. This study aimed to address this.

Questionnaires asking about sleepiness, behaviour and symptoms of OSAHS were sent to UK adults aged 16 years and over with DS and their relative or carer. Everyone returning a questionnaire was invited to have a sleep study at home to test for OSAHS. Everyone with symptoms and features of OSAHS on the home sleep study was invited to take part in a trial of CPAP, and they were then chosen at random to receive either continuous positive airway pressure (CPAP) or lifestyle advice, with review at 1, 3, 6 and 12 months. Individuals in the lifestyle group were offered CPAP after 1m. We measured sleepiness, behaviour, daytime function and general health at each visit.

We sent out 5270 questionnaires, of which 21% were completed and returned. People who replied were, on average, overweight/obese young adults. Just over half (55%) were men. Symptoms of OSAHS were similar in men and women, and sleepiness scores were broadly within the normal range. The questionnaire suggested that around 35% of adults with DS may have OSAHS. Those who might have OSAHS were sleepier, had more problem behaviour and had more symptoms than those unlikely to have OSAHS. Of the 790 individuals invited to participate in the treatment study, 149 had sleep studies, of which 134 were successful. There were no significant differences in sleep study results between men and women. Forty-two percent were diagnosed with OSAHS using the sleep study results. Twenty-eight adults with DS (19 men, 9 women) took part in the treatment study, 14 per group – again, these were overweight/obese young adults, this time with mild/moderate

sleepiness. By 12m, 4 participants had withdrawn, and all the remaining participants were on CPAP. Sleepiness and behaviour improved significantly with CPAP use, as did scores on a test of verbal intelligence.

This study estimates that 35-42% of adults with DS may have OSAHS - around 10 times more than in the general adult population. CPAP therapy is effective in adults with DS, with improvements in sleepiness, daytime function and behaviour maintained over a 12m period. Results suggest that a larger trial of CPAP in adults with DS may be required to assess other possible benefits.

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Abbreviations

Aβ	Beta-amyloid
ACTB	Arizona Cognitive Test Battery
ADHD	Attention deficit hyperactivity disorder
AH	Apnoeas/hypopnoeas per hour in bed
AHI	Apnoea/hypopnoea index per hour of sleep
AASM	American Academy of Sleep Medicine
ATC-DDD	Anatomical Therapeutic Chemical Classification System
AWI	Adults with incapacity
BMI	Body mass index
CRF	Case report form
DBC	Developmental Behaviour Checklist
DBC-A	Developmental Behaviour Checklist for Adults
DS	Down syndrome
DSA	Down's Syndrome Association
DSM-V	Diagnostic and Statistical Manual of Mental Disorders – 5th Edition
CPAP	Continuous positive airway pressure
EDS	Excessive daytime somnolence
ESS	Epworth Sleepiness Scale
EQ-5D	EuroQol 5-dimension questionnaire
GHQ-12	General Health Questionnaire – 12 item version
GP	General Practitioner
HLA	Human leukocyte antigen
HSA21	Human chromosome 21

ID	Intellectual disability
IQ	Intelligence quotient
KBIT-2	Kaufmann Brief Intelligence Test – 2nd Edition
LTP	Long-term potentiation
MAD	Mandibular advancement device
MSLT	Multiple sleep latency test
NADS	National Association for Down Syndrome
ODI	Oxygen desaturation index
OSA	Obstructive sleep apnoea
OSAHS	Obstructive sleep apnoea/hypopnoea syndrome
PAL	Paired Associates Learning
pESS	Pictorial Epworth Sleepiness Scale
PSG	Polysomnography
R&K	Rechtshaffen and Kales
RAND-36	RAND Corp. 36-item health-related quality of life questionnaire
RCT	Randomised controlled trial
REC	Research Ethics Committee
REM	Rapid eye movement
RN	Registered Nurse
RPSGT	Registered Polysomnographic Technologist
RSV	Respiratory syncitial virus
SDB	Sleep-disordered breathing
SIB-R	Scales of Independent Behavior – Revised
SIGN	Scottish Intercollegiate Guidelines Network

SpO_2	Oxygen saturation
SRT	Simple Reaction Time
UARS	Upper airways resistance syndrome
UK	United Kingdom
UPPP	Uvulopalatopharyngoplasty
USA	United States of America
WHO	World Health Organisation
ZBI	Zarit Burden Inventory

Chapter 1: Down syndrome: an overview

First described by J. Langdon Down in 1866 (Down 1866), Down syndrome (DS) is one of the commonest congenital conditions world-wide. This chapter provides an overview of the genetic basis, prevalence and impact of DS.

1.1 Genetic basis of DS

DS is an aneuploid disorder of human chromosome 21 (HSA21). An additional copy of HSA21 (trisomy 21) in the cells of individuals with DS was first identified by Jérôme Lejeune and colleagues in 1959 (Lejeune et al. 1959), and the majority of people with DS have this trisomy 21 karyotype. HSA21 is the smallest human chromosome, constituting only 1-1.5% of the human genome (Hattori et al. 2000); however, an additional copy of this small portion of the genetic blueprint has significant impact on the human phenotype.

Trisomy 21 most commonly arises due to nondisjunction during gametogenesis in one of the parents (more often the mother). DS can also arise from translocation of HSA21, where part of an additional HSA21 is fused to or transposed with another chromosome and present in all cells (Polani et al. 1960), or by mosaicism, where some, but not all, cells in the individual have an additional copy of HSA21 (Clarke et al. 1961). True Trisomy 21 is found in approximately 95% of individuals with DS, translocation in 4% and mosaicism in 1% (Sherman et al. 2007). Despite these differences in the genetic basis of DS, “Trisomy 21” is commonly used interchangeably with DS to describe the condition. For consistency and accuracy, the term “Down syndrome” (DS) is used throughout this thesis.

Figure 1: Female human trisomy 21 karyotype, with triple copy of HSA21 highlighted. Adapted by permission from Macmillan Publishers Ltd: NATURE REVIEWS GENETICS (Stylianos E. Antonarakis, Robert Lyle, Emmanouil T. Dermitzakis, Alexandre Reymond & Samuel Deutsch, Chromosome 21 and Down syndrome: from genomics to pathophysiology, Nature Reviews Genetics, 5, 725-738), copyright (2004).

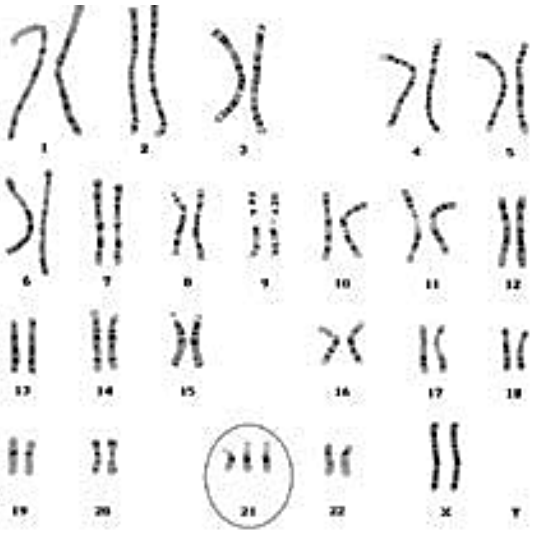
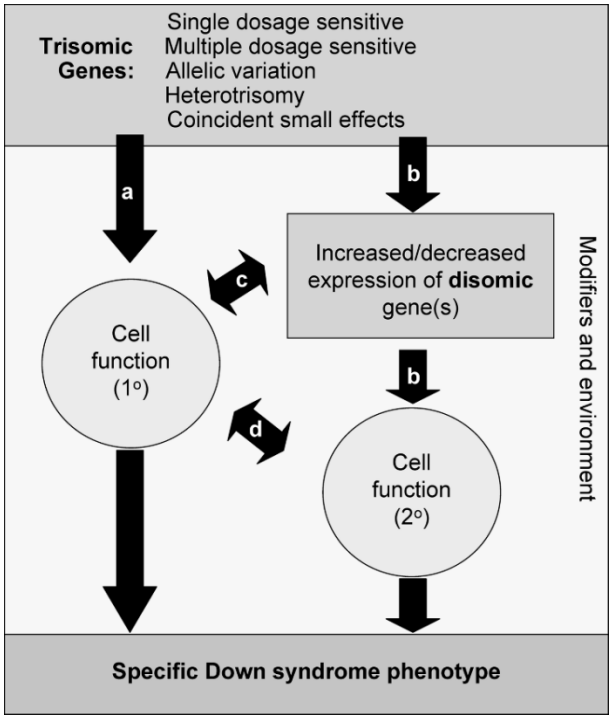


Figure 2: Possible phenotypic consequences of gene action in Down syndrome. From Roper RJ, Reeves RH (2006) Understanding the Basis for Down Syndrome Phenotypes. PLoS Genet 2(3): e50. Reproduced under the terms of the Creative Commons Attribution License.



Although DS arises from broadly the same genetic mutation – that is, a 50% increase in expression of the genes of HSA21 - wide phenotypic variation is observed in individuals with DS. This is likely due to the interaction of the triplicated genes of HSA21 with the non-trisomic genes of the remaining chromosomes, along with environmental factors – see

Figure 2 (Roper & Reeves 2006). It is important to remember that familial and ethnic characteristics will be expressed alongside those related to DS; for example, although there are recognisable facial characteristics associated with DS, individuals also show a resemblance to other family members (Dierssen et al. 2009).

1.2 Epidemiology

1.2.1 Prevalence

DS is a common disorder, affecting around 1 in 1000 live births world-wide (World Health Organization 2015). However, prevalence varies with a number of factors including maternal age, country and ethnicity, and can be ascertained in a number of ways.

1.2.1.1 Live birth prevalence

Despite the introduction of routine screening for DS during pregnancy in recent decades and a rise in termination rates, the birth rate has remained steady across Europe at around 1 in 1000 live births (Dolk et al. 2005; Loane et al. 2013).

In Scotland, a cytogenetic register has recorded data on all trisomies, including DS, since 1989. From 1989-1991, live birth prevalence was estimated at 1.2 per 1000, with no significant regional variations (Carothers 1994). A similar register collecting data on DS in England and Wales was also founded in 1989. At this time, DS prevalence was 1.10 per 1000 live births, falling by 1% to 1.08 in 1000 in 2008, due to antenatal screening and subsequent termination (Morris & Alberman 2009). It is estimated that around 700 babies are born with DS in England and Wales every year (Charleton et al. 2010).

Live birth rate in the US is similar to that of the UK and Europe. Estimated live birth prevalence has increased over time, from 0.9 per 1000 live births in 1979 to 1.2 per 1000 in 2003 (Shin et al. 2009), with an estimated 1.4 in 1000 live births in the period 2004-2006 (Parker et al. 2010).

The two main factors which determine the live DS birth rate are the true incidence of DS, which is influenced by the distribution of maternal age, and the rate of termination of pregnancy secondary to antenatal screening (Morris & Alberman 2009). Data from a European network of DS data registries shows that the percentage of DS live births to women aged ≥35 years has risen steadily, from 8% in 1980 to 13% in 1990 and 19% in 2009 (Dolk et al. 2005; Loane et al. 2013). Similar trends were noted in the North of England, rising from 6% in 1985 to 15% in 2004 (Irving et al. 2008), and in Victoria, Australia, rising from 8% in 1986 to 23% in 2004 (Collins et al. 2008). However, although the prevalence of DS rises with maternal age, this reaches a plateau at around 45 years of age (Morris et al. 2002).

Countries in which termination of pregnancy is illegal consequently have a higher live birth rate, averaging 1.6 per 1000 in Malta and 2.0 per 1000 in Ireland (Dolk et al. 2005). Where termination is available, the rate of uptake varies with maternal age, gestational age at diagnosis and ethnicity (Natoli et al. 2012).

Studies of ethnically-diverse states in the US have compared the prevalence of DS among ethnicities. Two studies in California noted a higher DS birthrate in Hispanic women compared with white women of European origin, particularly in younger mothers (Bishop et al. 1997; Hook et al. 1999). A further study in Hawaii found ethnic variation in live birth rate, ranging from 0.8 per 1000 in African-Americans, Hawaiians and Samoans, to 2.4 per 1000 in Koreans, against an overall prevalence of 0.8 per 1000 (McDermott & Johnson 2011). Although there are few studies of DS in Africa, live birth prevalence of DS has been estimated in the region of 1.2-1.8 per 1000 (Christianson 1996). Prevalence in Japan appears to be lower than the worldwide average, at 0.6 per 1000 live births (Hoshi et al. 1999), though a prevalence of 1.7 per 1000 was noted in Japanese mothers living in Hawaii (McDermott & Johnson 2011). However, a review of 36 studies covering 49

populations worldwide found that, once standardised for maternal age, the variation in prevalence between populations was only ±25%, though the increased rates in Hispanic mothers may remain (Carothers et al. 1999).

1.2.1.2 Total prevalence

Ascertainment of total prevalence takes into account not just the number of live births affected by DS, but also the number of stillbirths and late foetal deaths and the termination of pregnancy for foetal abnormality following an antenatal diagnosis of DS.

In a study of 12 countries across Europe, the total prevalence during the period 1990-2009, corrected for these outcomes, averaged 2.2 per 1000 births, versus a live birth prevalence of 1.1 per 1000 (Loane et al. 2013). While the total prevalence increased across this period, the live birth rate remained essentially stable. The stability of live birth rates across Europe suggests that the rise in mean maternal age, giving rise to an increase in the number of DS pregnancies, is counterbalanced by an increased termination rate.

Data from the England and Wales National Down Syndrome Cytogenetic Register shows that, whilst live birth prevalence remained relatively steady between 1989 and 2008, the number of DS diagnoses increased by 71%; during this period, the percentage of women opting to terminate their pregnancy after an antenatal diagnosis of DS remained stable at 92% (Morris & Alberman 2009). Interestingly, the total prevalence of DS in the USA including live births, still births and terminations was 1.6 per 1000, differing only slightly from the live birth prevalence and prevalence of live and stillbirths combined, both of which averaged 1.4 per 1000 (Parker et al. 2010). This would suggest either a lower rate of antenatal detection or uptake of elective termination than elsewhere in the world, though the reasons for this are unclear.

1.2.1.3 Population prevalence

Fewer studies have attempted to document the population prevalence of individuals living with DS. The population prevalence in England and Wales was estimated at

0.7 per 1000 people in 2011, equating to over 37,000 people in England and Wales and over 47,000 in the whole of the UK (Wu & Morris 2013). Similarly, a study in the USA estimated that DS affected 0.8 in 1000 people, with over 250,000 living with DS in 2008 (Presson et al. 2013). In 2002, a further US study estimated that the prevalence of DS in children and adolescents aged 0-19 years was 1.0 in 1000; that is, over 83,000 young people in the USA alone (Shin et al. 2009).

1.2.2 Life expectancy of people with DS

As recently as 1983, the median age of death for people with DS was 25 years (Yang et al. 2002). However, life expectancy has increased steadily; in 2011, 37% of people with DS in England and Wales were aged >40 years, and the median life expectancy for a baby born that year was an estimated 58 years (Wu & Morris 2013). Life expectancy in a cohort of people with DS in Western Australia was 59 years, with a quarter of individuals living to 63 years and the oldest into their 70s (Glasson et al. 2002). This improved life expectancy is in part related to the early treatment of health problems, with an overall one-year survival rate of 90%, rising to 97% in those without congenital heart problems (Irving et al. 2008; Coppus 2013). Given the comorbidities associated with DS, which are discussed in more detail in Section 1.3.2, the ageing population of individuals with DS has important implications for health and social care services.

1.3 The DS phenotype

Although all cases of DS result from essentially the same underlying genetic cause, there is a broad spectrum of phenotypic expression (see

Figure 2), and a wide range of features and comorbidities are associated with the condition. This section outlines these features, highlighting the similarities and differences between individuals with DS. Given the topic of this thesis, special consideration will be given to sleep disturbances associated with DS.

1.3.1 Physical features

DS is characterised by a widely-recognised set of physical features, many of which were described in Down's original observations of 1866 and formed the basis of identification of DS prior to the advent of genetic testing (Down 1866). A checklist of 25 features, subsequently narrowed down to the 10 most useful discriminating factors, was used by Jackson et al to identify DS in children suspected of having the disorder prior to cytogenetic analysis (Jackson et al. 1976) – see Table 1. Using the 10-feature checklist, almost three-quarters of the children tested were correctly classified, with a false positive rate of 4.6% and a false negative rate of 12.2%. A "phenotypic map", detailing the genes suspected to be responsible for many of these physical features has since been constructed (Korenberg et al. 1994). Postmortem analysis has allowed further characterisation of internal and external morphological features commonly found in individuals with DS (Byard 2007). Although the characteristic features of DS are evident in individuals with mosaic DS, these tend to be more subtle, reflecting the proportion of cells with an additional HSA21 chromosome (Papavassiliou et al. 2009; Hultén et al. 2013).

Of course, it is important to bear in mind that, despite these characteristic features, there are many more differences between individuals with DS than there are similarities, with individuals resembling their parents more than each other. Although there is trisomy of HSA21, other traits related to the rest of the genotype will still be expressed (Dierssen et al. 2009).

1.3.1.1 Short stature

Short stature is a common feature of nearly all individuals with DS (Roizen & Patterson 2003; Byard 2007). The reasons for this are unclear in most, although poor growth can be secondary to some of the comorbidities associated with the condition, including congenital heart disease, thyroid dysfunction and coeliac disease, as well as upper airway resistance, which will be discussed in greater detail in Chapter 2 (Styles et al. 2002).

DS-specific growth charts have been published for the UK and Republic of Ireland, US and Sweden, documenting observed (but not necessarily desirable) height and

weight in children with DS (Cronk et al. 1988; Styles et al. 2002; Myrelid et al. 2002). The average height of men with DS is 157cm, and of women, 145cm (Charleton et al. 2010), significantly lower than the general UK population averages of 175cm and 162cm for men and women respectively (Office for National Statistics 2010).

Table 1: Jackson's 25 signs of Down syndrome, with the ten most distinguishing features highlighted *. (Adapted from Jackson et al. 1976)

Brachycephaly *	Folded ear *
Oblique eye fissure *	Short neck *
Epicanthic eye fold	Loose skin of neck
Blepharitis/conjunctivitis	Short and broad hands
Brushfield spots	Short fifth finger
Nystagmus *	Incurved fifth finger *
Flat nasal bridge *	Transverse palmar crease
Mouth permanently open	Gap between first and second toes *
Abnormal teeth	Congenital heart defect
Protruding tongue	Murmur
Furrowed tongue	Joint hyperflexibility
High arched palate	Muscular hypotonia *
Narrow palate *	

1.3.1.2 Obesity

Obesity is common in individuals with DS. Children with DS are commonly overweight by the age of 4 years (Roizen & Patterson 2003), with one study of

children in the UK and Republic of Ireland finding that, by the age of 10, 30% were overweight and 20% were obese; that is, above the 91st and 98th centiles for the general population respectively (Styles et al. 2002). This trend continues into adulthood, with obesity evident in 20-77% of adults with DS (Prasher 1995; Van Allen et al. 1999; Melville et al. 2005; Melville et al. 2007; Henderson et al. 2007).

The tendency towards overweight and obesity may be related, at least in part, to short stature, though the cause is multifactorial. Obesity appears to be more prevalent in women, but not men, with DS, compared with adults with ID due to other causes (Melville et al. 2005). A further study by the same group noted that the risk of being overweight or obese decreased with increasing severity of ID (Melville et al. 2005; Melville et al. 2007). Of course, common comorbidities of DS which can impact on weight gain, such as hypothyroidism, should be screened for across the lifespan (Van Allen et al. 1999; Roizen & Patterson 2003; Bull 2011).

Residential status may be important; in the Scottish study discussed above (Finlayson et al. 2009), residential setting was a significant factor impacting on low levels of physical activity; living in a congregate care setting was a significant predictor of low levels of physical activity. Living in the family home has been associated with increased risk of being overweight or obese in comparison to supervised care or hospital in a previous study in the US (Prasher 1995).

Obesity is a major risk factor for sleep-disordered breathing in both adults with DS and the general population, and this is discussed further in Chapters 2 and 3.

1.3.1.3 Premature ageing

Premature ageing is a characteristic feature of adults with DS. 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 hearing and visual impairment (Esbensen 2010; Coppus 2013), which are discussed elsewhere in this chapter. One of the most striking and common features of premature ageing in adults with DS is early-onset dementia, similar to Alzheimer's disease, and, again, this is discussed in further detail later in the Chapter.

1.3.2 Comorbidities

Although general health varies widely between individuals with DS, there are a range of comorbidities which occur more frequently in the DS population across the lifespan (Charleton et al. 2010).

1.3.2.1 Cardiovascular comorbidities

Congenital heart defects, including atrial and/or ventricular septal defects, are common in individuals with DS. Reported prevalence rates at birth range from 40% to 75% (Irving et al. 2008; Vis et al. 2009; Charleton et al. 2010; McDermott & Johnson 2011), with possible gender and ethnic differences evident (Yang et al. 2002; Vis et al. 2009). Better treatment of congenital heart disease in early life has been a significant contributor to the increased life expectancy of individuals with DS (Coppus 2013), although, in one study, 13% of deaths in children and young people with DS aged <18 years were attributed to congenital heart defects (Bittles et al. 2002). Two cohort studies estimate that 14-16% of adults with DS have untreated congenital heart defects (Van Allen et al. 1999; Henderson et al. 2007). Patients with DS are at an increased risk of pulmonary arterial hypertension, which is present in around 51% of children and 8% of adults with the condition (Van Allen et al. 1999; Vis et al. 2009; Hawkins et al. 2011; Sharma et al. 2013). This can be related to uncorrected cardiac defects, with children with DS developing pulmonary hypertension sooner than children with similar abnormalities but without DS (D'Alto et al. 2013). Of importance to the current study, pulmonary hypertension can also result from or be exacerbated by upper airway obstruction, and this is discussed in more detail in Chapter 2.

1.3.2.2 Dermatological issues

Dermatological problems, such as dry skin, atopic and seborrhoeic dermatitis and fungal infections of the nail and skin, are common in people with DS (Schepis et al. 2002; Madan et al. 2006). One community-based survey in the UK found eczema in 23% of adults with DS (Henderson et al. 2007), and a retrospective study of adults with DS in the US found 26% of individuals had a skin disorder of some type (Kerins et al. 2008).

1.3.2.3 Endocrine dysfunction

Thyroid dysfunction, particularly hypothyroidism, is common in individuals with DS (Prasher 1999). It can be present from birth; 1% of newborns with DS will have congenital hypothyroidism, compared with 1 in 4000 in the general population (Roizen & Patterson 2003; Bull 2011). Hyperthyroidism may also occur, though less commonly so, in around 2% of adults with DS (Prasher 1999; Charleton et al. 2010).

1.3.2.4 Gastrointestinal comorbidities

Congenital abnormalities of the gastrointestinal tract, such as gastrointestinal atresia, are evident in 7-12% of children with DS, and are usually picked up and corrected shortly after birth Coeliac disease, an autoimmune disorder triggered by gluten ingestion, occurs in 5-7% of individuals with DS, with a mean diagnostic delay of 3.8 years from onset of symptoms (Roizen & Patterson 2003; Bull 2011).

1.3.2.5 Haematological problems

Although overall rates of cancer are lower in DS than in the general population, incidence of leukaemia is increased, estimated to affect 1-2%; studies have reported a 14-22 times increase in risk generally (Van Allen et al. 1999; Goldacre et al. 2004; Byard 2007; Charleton et al. 2010), rising to 60 times in those aged ≤4 years (Sullivan et al. 2007). Leukaemia is a common cause of mortality in children with DS, and carries a standardised mortality odds ratio of 1.6 (Yang et al. 2002). However, risk decreases with age (Esbensen 2010).

1.3.2.6 Immunological disorders

Individuals with DS often have impaired immune function from birth, which can lead to recurrent bacterial and viral infections (Charleton et al. 2010). Increased prevalence of a number of autoimmune disorders has been noted, including coeliac disease, autoimmune thyroiditis, leukaemia, type 1 diabetes, autoimmune hepatitis and skin conditions such as vitiligo and alopecia areata.

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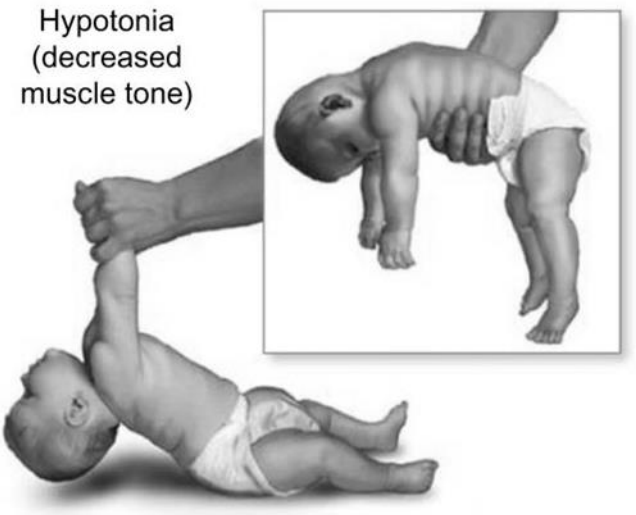
1.3.2.7 Musculoskeletal disorders

Around a fifth of individuals with DS have associated musculoskeletal disorders (Mik et al. 2008). Collagen is an important protein present in muscles, ligaments and tendons, constituting up to 6% of muscle tissue. The genes for type VI collagen are located on HSA21; type VI collagen is of particular importance in formation of skeletal and cardiac muscle, which may be related to the musculoskeletal and cardiac defects noted in individuals with DS (Dey et al. 2013).

Generalised hypotonia (see

Figure 3), related to abnormal development of the cerebellum, is evident in individuals with DS, who present as "floppy babies" at birth (Lott 2012). Hypotonia continues into adulthood, and older adults with DS tend to have greater muscle weakness than others with ID and the general population.

Figure 3: Generalised hypotonia in a baby with Down syndrome. Note the head lag upon pull to sitting and the inability to support posture in ventral suspension. Reprinted from Progress in Brain Research, Vol. 197, Lott IT, Neurological phenotypes for Down syndrome across the life span, Pages No. 101-121, Copyright (2012), with permission from Elsevier.



1.3.2.8 Neuropsychiatric morbidity

Children and adults with ID are more than twice as likely to experience behavioural and emotional disturbances than the general population, with around 40% of these reaching a clinically concerning level. Around 18% of children with DS have a psychiatric disorder, rising to 26-30% in adults. Attention deficit hyperactivity disorder (ADHD) and obsessive-compulsive disorder are commonly seen in children and adolescents. Around 10% of individuals with DS have a dual diagnosis of autism (Kent et al. 2007; Smith 2001; Roizen & Patterson 2003; Dykens 2007; Virji-Babul et al. 2007; Bull 2011).

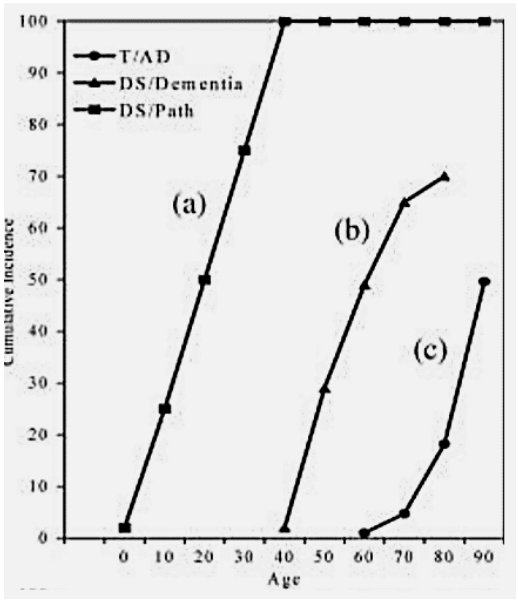
Depression and anxiety occur frequently in adults with DS; one study reported depression or anxiety in 38% of adults aged 31-40 years and 46% of those ≥40 years (Virji-Babul et al. 2007), whilst another found anxiety and/or depression in 34% of under 50s and 22% in those aged ≥50 years (Kerins et al. 2008). Other studies have reported more modest rates of around 6-18% (Holland et al. 1998; Roizen & Patterson 2003; McCarron et al. 2005; Mantry et al. 2007). Early-onset dementia, similar to Alzheimer's disease, is well-described in the literature, and is of particular relevance given the increasing life expectancy of individuals with DS. It is the most common cause of morbidity and mortality in adults with DS, with a standardised mortality odds ratio of 21.1 (Yang et al. 2002; Coppus 2013). Overall prevalence is estimated at 13-24% (Strydom et al. 2010), but it is clear that prevalence of dementia in adults with DS increases significantly with age: 3-10% at 30-39 years; 8-25% at 40-49 years; 28-55% at 50-59 years; 30-75% at 60-69 years and 100% at ≥70 years (Lai & Williams 1989; Visser et al. 1997; Holland et al. 1998; Van Allen et al. 1999; Smith 2001; Strydom et al. 2010). Although a clinical diagnosis of dementia is not made in the majority of individuals until their early-to-mid 50s (Lai & Williams 1989; Roizen & Patterson 2003), virtually all adults with DS will have neuropathological markers of dementia in the brain by the age of 40 (Lai & Williams 1989; Van Allen et al. 1999; Lott & Head 2005; Dykens 2007; Zigman & Lott 2007; Urv et al. 2008).

There is clearly a period during which pre-clinical changes are occurring in the absence of overt symptoms of dementia, and number of prodromal symptoms have

been described. Emotional disturbances, depression and changes in behaviour and personality may precede both problems with memory and confusion, and dementia *per se*; the number and severity of maladaptive behaviours increases with progression of dementia, and individuals showing sub-clinical changes in personality and behaviour are 1.5 times more likely to go on to develop dementia within 5 years (Ball et al. 2006; Dykens 2007; Urv et al. 2008; Lott & Dierssen 2010).

Despite the high prevalence of dementia in adults with DS, few studies have evaluated treatment in this group (Lott & Dierssen 2010). Most recently, a randomised, placebo-controlled trial of memantine – a drug known to improve cognitive function in older adults with Alzheimer's disease in the general population – failed to show an improvement in adults ≥40 years with DS (Hanney et al. 2012).

Figure 4: Cumulative incidence of (a) Alzheimer's disease type neuropathology in the DS population, (b) Alzheimer's disease dementia in the DS population and (c) Alzheimer's disease dementia in the typically-developing population. Copyright 2007, Wiley. Used with permission, from Zigman WB and Lott IT, MRDD Research Reviews 2007;13:237–246



1.3.2.9 Respiratory comorbidities

As previously noted, individuals with DS often experience frequent respiratory tract infections, related to immunodeficiency and structural abnormalities of the airways (Kusters et al. 2009; Ram & Chinen 2011). Generalised hypotonia can lead to malacia of the airways, which can impact on breathing and increase the risk of respiratory infection due to reduced mucus clearance. Sensory problems

Hearing and visual impairment are common in individuals with DS at every age. There is evidence of premature ageing, with early onset of age-related hearing loss and senile cataracts, and an increasing prevalence of hearing and visual impairment with age (McCarron et al. 2005; Esbensen 2010; Torr et al. 2010). Regular screening across the lifespan is recommended (Henderson et al. 2007; Charleton et al. 2010; Bull 2011).

Importantly, it should be noted that sensory impairment can manifest as behavioural and emotional disturbances in individuals with DS due to diminished communication skills; an individual who cannot hear may appear stubborn, ignorant or withdrawn (Smith 2001; Määttä et al. 2006). However, sensory impairment was not associated with mental ill-health in one cohort of adults with DS (Mantry et al. 2007). Learning and cognitive function may be affected by visual or hearing loss (Lott 2012).

1.3.3 Protective effects of DS

Although associated with a range of comorbidities, there is evidence that DS may have a protective effect in other areas.

1.3.3.1 Cancer

Rates of most common cancers (excluding leukaemia and testicular cancer) are significantly lower in individuals with DS, and tumour-suppressing genes have been identified on HSA21 (Yang et al. 2002; Bittles et al. 2002; Kerins et al. 2008; Xavier et al. 2009; Esbensen 2010).

1.3.3.2 Hypertension

Hypertension is very uncommon, affecting only 0-3% of adults with DS in a number of studies (Van Allen et al. 1999; Kerins et al. 2008; van de Louw et al. 2009). This

is much lower than is seen in adults with other forms of ID, estimated at around 17% (van de Louw et al. 2009). Prevalence of hypertension in the general population worldwide is estimated at 26% (Kearney et al. 2005).

1.3.3.3 Ischaemic heart disease

While the incidence of congenital heart disease is high in adults with DS, ischaemic heart disease is much less common in this population, occurring in 0-13% (Van Allen et al. 1999; Bittles et al. 2002; Kerins et al. 2008; Esbensen 2010; Coppus 2013). Atherosclerotic protective factors have been associated with genes located on HSA21, and are over-expressed in DS, which may explain the low rates of atherosclerosis in this population (Vis et al. 2009).

Reduced exposure to environmental and social factors with known associations with these diseases may play a protective role, with rates of alcohol and tobacco use very low in adults with DS and ID of other causes, in comparison with the general population – 45-96% are non-drinkers and 85-100% non-smokers (Robertson et al. 2000; Jobling & Cuskelly 2009; Haveman et al. 2011; de Winter et al. 2009).

1.3.3.4 The "Down syndrome advantage"

DS may confer a benefit to other members of the family. A "Down syndrome advantage" has been well-described in the literature; mothers of children with DS tend to display better psychological wellbeing (including lower stress levels, more close and harmonious family relations, less pessimism and less caregiver burden) than mothers of children with other developmental disabilities and ID, across the lifespan of their son or daughter (Hodapp et al. 2001; Esbensen & Seltzer 2011). This may be related to a number of factors, the most important of which may be the behavioural phenotype of the person with ID; higher levels of problem behaviour were associated with poorer relationship quality and greater maternal pessimism, and behaviour problems are a stronger predictor of maternal well-being than functional abilities.

1.3.4 Intellectual disability in individuals with DS

Alongside the characteristic physical phenotype, one of the hallmark features of DS is intellectual disability (ID). DS is the most common genetic cause of ID world-wide. The most recent edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) defines "intellectual disability" as impairment of general mental abilities that impact adaptive functioning in the conceptual, social and practical domains, originating in the developmental period (American Psychiatric Association 2013). This replaces the term "mental retardation", which is now generally considered both outdated and offensive. ID can be classified as mild, moderate, severe or profound, based on the level of adaptive functioning displayed by the individual. Although intelligence quotient (IQ) test scores were previously used as a cut-off for ID level, this is no longer the case, with more emphasis placed on overall functioning.

1.3.4.1 IQ

Individuals with DS can exhibit a wide range of IQ, typically from around <20 to 70, with most in the moderate to severe range (Dierssen et al. 2009; Mégarbané et al. 2013). As mentioned above, IQ no longer forms a part of the formal diagnostic criteria for DS in DSM-5, but IQ testing is still recommended as part of an individual's assessment; in DSM-5, ID is typically considered to be approximately two standard deviations below the general population average, which is equivalent to an IQ score ≤70.(American Psychiatric Association 2013). Individuals with mosaic DS have significantly higher IQ than those with trisomy 21 (Fishler et al. 1991). IQ typically diminishes with age in the general population; a number of studies have reported that this process is amplified in adults with DS, though only in verbal, not performance, IQ (Carr 2005).

1.3.4.2 Neurological basis of ID in DS

A number of characteristic changes occur in the structure and functioning of the brain in individuals with the DS. The overall volume of the brain is over 20% smaller than that of typically-developing individuals, despite controlling for reduction in body size (Contestabile et al. 2010). Although some studies suggest this change is evident from the prenatal period an persists into adulthood (Contestabile et al. 2010;

Lott 2012), others suggest that brain size is normal at birth, with the relative reduction in size occurring postnatally by around 6 months of age (Fidler & Nadel 2007). Regardless, it is clear that there is an overall shortening of the brain (brachycephaly) and reduced total brain volume, with reduced volumes in a number of brain areas including the frontal and temporal lobes, hippocampus and cerebellum, and that these areas continue to be most affected across the lifespan (Nadel 2003). Reduction in cerebellar volume may be related to growth restriction imposed by the small cranial vault associated with DS.

As well as volumetric changes, abnormal development and functioning of the brain has been noted. A study of over 100 brains of children with DS found a delay in myelination in around a quarter of children, in comparison with 7% of children without DS; this was particularly evident in nerve fibres linking the frontal and temporal lobes (Wisniewski 1990; Nadel 2003). A number of studies, in both DS and ID of other aetiology, have reported abnormal development of dendrites, neuronal structures which are vital for synaptic connectivity and brain plasticity. Dendrites are shorter and show less branching in the hippocampus and cortex of individuals with DS, worsening with age (Contestabile et al. 2010). Minicolumns, the functional units of the cerebral cortex, are larger and less dense in individuals with DS (Dierssen et al. 2009). Decreased levels of neurotransmitters have been noted, both during foetal development and later in life (Contestabile et al. 2010). As discussed earlier, beta-amyloid plaques and neurofibrillary tangles develop much earlier in individuals with DS than in the general population (Lott 2012).

To summarise, a combination of neuropathological factors – including a reduced number of neurons, abnormal neuronal structure and accelerated degeneration – contribute to the ID seen in DS, with some brain regions more affected than others. The relationship between these regional changes and the cognitive phenotype of individuals with DS will be discussed in the following sections.

1.3.4.3 Motor function

Children with DS experience delay in gross motor functions such as rolling, sitting, walking and running (Palisano et al. 2001), and impaired motor function is evident in

a number of mouse models of DS (Contestabile et al. 2010). This delay in motor development appears to be more pronounced than the delay in intellectual development (Volman et al. 2007), though motor growth curves show that the limit appears to be the rate of development and not the level of skills which can be acquired, with more complex movements requiring more time to learn (Palisano et al. 2001). This is, in part, related to generalised hypotonia (see Section 1.3.2.7), with a higher degree of hypotonia related to worse motor function (Volman et al. 2007).

1.3.4.4 Speech and language

The development of speech and language is delayed in children with DS, in comparison with both typically-developing children and those with ID due to other causes (Kernan & Sabsay 1996). This is related to hearing and visual impairments, oromotor dysfunction and orofacial anatomical abnormalities, as well as ID *per se* (Roberts et al. 2007; Martin et al. 2009). However, most individuals with DS develop at least basic language skills, with many adults with DS being able to communicate successfully during their daily routines (Kernan & Sabsay 1996).

Language deficits in individuals with DS may be related to problems with short-term memory (Chapman & Hesketh 2001), and this is discussed further below.

1.3.4.5 Learning and memory

There is a huge wealth of literature devoted to learning and memory in individuals with DS, which is perhaps unsurprising given the prominence of ID as a feature affecting all people with DS. The neurological basis of the learning and memory deficits observed in individuals with DS is summarised in Figure 5 (Lott & Dierssen 2010). This section will focus predominantly on the three main brain areas which have been identified as being most affected in DS – the hippocampus, prefrontal cortex and cerebellum (Nadel 2003).

To fully understand the impairment observed in individuals with DS, a basic review of the categorisation of memory processes is required, and follows herewith, adapted from a description by Robert Stickgold (Stickgold 2005). A visual representation is shown in Figure 6. Memories are broadly divided into two categories: declarative,

which are facts that can be recalled; and non-declarative, which are unconscious memories. Declarative memories are further divided into memories of specific events (episodic) and general knowledge memories (semantic). Examples of these include what one had for dinner last night (episodic) and the capital city of France (semantic). Non-declarative memories are those which are used without conscious recollection, such as how to ride a bike. These are further sub-divided into procedural skills (step-by-step actions), conditioning (unconscious response to a stimulus), non-associative (habituation and sensitisation) and priming (related to prior exposure to an item, or a related item). All memories are formed through a process of acquisition, processing and storage, then recalled at a later date. Memory consolidation refers to the neurological processes by which acquired memories are stabilised and stored for future recall.

Figure 5: The learning circuit in DS. The flow diagram represents the stages of information flow relevant to learning and memory which have been reported to be altered in DS. Reprinted from The Lancet Neurology, Vol. 9, IT Lott and M Dierssen, Cognitive deficits and associated neurological complications in individuals with Down's syndrome, Page no. 623-33, Copyright (2010), with permission from Elsevier.

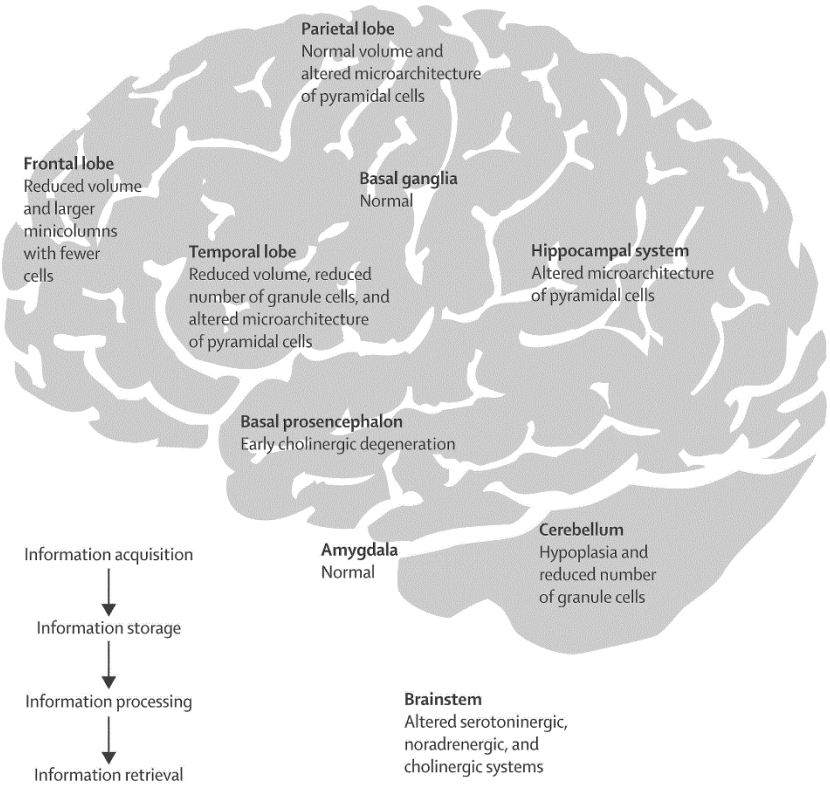
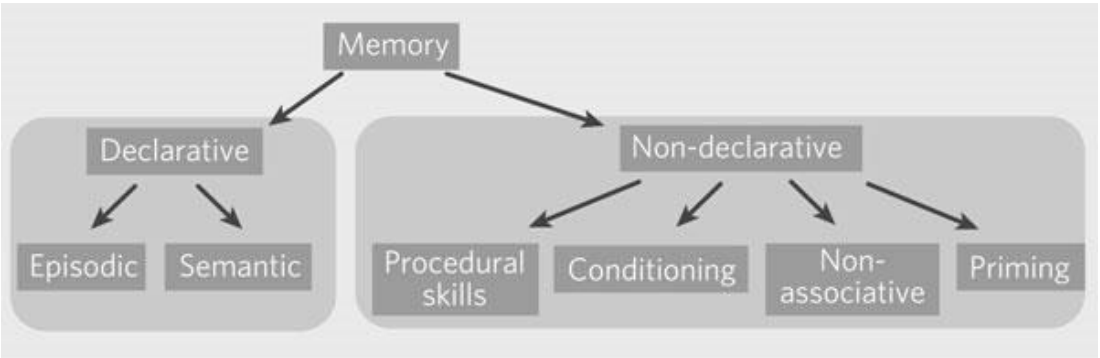


Figure 6: Categorisation of memory systems. Reprinted by permission from Macmillan Publishers Ltd: Stickgold R, Nature; 437, 1272-1278, copyright (2005)



The hippocampus is involved in declarative memory, and is important for flexible learning and consolidation of learning (Nadel 2003; Teipel & Hampel 2006; Dierssen et al. 2009). Spatial cognition also involves hippocampal function (Nadel 2003). Individuals with DS exhibit deficits in long-term storage, particularly encoding and retrieval, of declarative memory (Lott & Dierssen 2010). One study in children with DS found that, whilst they could acquire information almost as quickly as typically-developing children, they had problems retaining the information, suggesting hippocampal impairment. A further study in adolescents found specific evidence of hippocampal dysfunction, with individuals with DS performing worse than typically-developing controls on all five tests used (Wishart 1993; Pennington et al. 2003; Fidler & Nadel 2007). The volume of the hippocampus decreases with age in adults with DS, and is one of the first areas to be affected by accumulation of Aβ during the early stages of dementia. This is associated with a decline in memory function in those with and without dementia, and problems with learning, memory and visuospatial organisation in those with dementia (Teipel & Hampel 2006; Lott & Dierssen 2010).

The prefrontal cortex is of particular importance in executive function and working memory, and also has a role in episodic memory (Nadel 2003; Pennington et al. 2003). Impairment in working memory has been noted, particularly in verbal (but not visuospatial) information (Jarrold & Baddeley 2001; Fidler & Nadel 2007). Children with DS perform poorly on tests of executive function which require memory as well as visual-motor organisation (Dierssen et al. 2009).

The role of the cerebellum is less clear, though it appears to be involved in visual and motor skills, conditioning and higher order functioning such as emotion and affect. Problems with attention, learning, verbal fluency and working memory are also noted (Nadel 2003; Dierssen et al. 2009; Lott & Dierssen 2010). A battery of neuropsychological tests has been developed to measure prefrontal, hippocampal and cerebellar functioning in children and adults with DS (Edgin et al. 2010), and is discussed in more detail in Chapter 8.

1.3.5 Behaviour

A personality or behaviour stereotype of individuals with DS has persisted over time, with people with DS being perceived as exhibiting a host of positive personality traits, including cheerfulness and affection. This may be, in part, related to an increased use of nonverbal social gestures by children with DS (Fidler 2006) and the relatively low prevalence of maladaptive behaviours which adults with DS display in comparison with adults with ID of other causes (Chapman & Hesketh 2000; Blacher & McIntyre 2006). This personality stereotype may also contribute to the "DS advantage" discussed previously (Esbensen & Seltzer 2011). However, a wide variation in personality traits are exhibited by individuals with DS, and maladaptive behaviour and neuropsychiatric problems do occur (see Section 1.3.2.8 above). Specific behavioural phenotypes in individuals with DS have been described in some detail, and a summary of the emergence of these phenotypes with age is shown in

Table 2 (Chapman & Hesketh 2000).

Behavioural and emotional disturbances in adults with DS are commonly related to mental health problems, such as depression, pre-clinical and clinical symptoms of dementia and, of direct relevance to this thesis, sleep disorders (Capone et al. 2006; Dykens 2007).

1.4 Societal issues

As well as the physical, mental and emotional difficulties which can be associated with DS, there are a number of wider societal issues which people with DS and their families face.

1.4.1 Education

A detailed review of the educational needs of children and adolescents with DS is outwith the scope of this thesis. However, the inclusion of children with DS in mainstream schools is now commonplace in most developed countries; for example, inclusion in mainstream schooling has been in effect in Italy since the early 1970s

(Bertoli et al. 2011), and, by the mid-1990s, fewer than 2% of children in the UK were attending "special" schools (Farrell 2000). Mainstream education has been shown to have educational and social benefits for individuals with DS, with attendance at a mainstream school being a significant predictor of higher academic attainment (Laws et al. 2000; Buckley et al. 2006; Turner et al. 2008).

Table 2: Developmental emergence of the behavioural phenotype of Down syndrome. Copyright 2000, Wiley. Used with permission, from Chapman RS and Hesketh LJ. MRDD Research Reviews 2000; 6:84-95.

Age	Domain	Behavioral Phenotype
Infancy (0–4 years)	Cognition	Learning delays at ages 0–2 accelerating at ages 2–4
	Speech	No difference in vocalization types; slower in transition from babbling to speech; poorer intelligibility
	Language	Delays relative to cognition in frequency of nonverbal requesting, rate of expressive vocabulary development, rate of increase in mean length of utterances; but not comprehension
Childhood (4–12 years)	Cognition	Selective deficits in verbal short-term memory
	Speech	Longer period of phonological errors and more variability; poorer intelligibility
	Language	Expressive language delays continue relative to comprehension
	Adaptive behavior	Fewer behavior problems compared to controls with cognitive disability; more behavior problems than siblings without Down syndrome. Anxiety, depression, and withdrawal correlate positively with increasing age.
Adolescence (13–18 years)	Cognition	Deficits in verbal working-memory and delayed recall
	Speech	More variability in fundamental frequency, rate control, and placement of sentential stress
	Language	Expressive language deficit in syntax greater than expressive language deficit in the lexicon Comprehension of words typically more advanced than nonverbal cognition Syntax comprehension beginning to lag nonverbal cognition
	Adaptive behavior	Fewer behavior problems compared to controls with cognitive disability Anxiety, depression, and withdrawal correlate positively with increasing age
Adulthood (over 18 years)	Cognition	Behavioral symptoms of dementia beginning to emerge at 50 years for up to 50%
	Speech	Higher incidence of stuttering and hypernasality
	Language	Comprehension of syntax continues to lag cognition
	Adaptive behavior	Fewer maladaptive behaviors than controls with cognitive disability Higher rates of depression with increased age Dementia in Down syndrome is not associated with increased rates of aggression

1.4.2 Employment

The transition from school can be particularly challenging for young people with DS, who may face additional barriers to employment due to their ID and comorbidities, as well as perceptions relating to their abilities; one survey of over 2000 people in the general population in Australia found that only 39% thought that an adult with DS was likely to be able to work independently in paid employment (Gilmore et al. 2003).

1.4.3 Daily living

A number of options are available to individuals with DS, ranging from fully independent accommodation, supported accommodation, group homes and communities to residential care settings. However, an individual's level of independence and ID may determine their living arrangements to a certain extent. Individuals with DS in residential care commonly have more comorbidities, and accommodation setting may be related to health outcomes including poor diet, obesity and inactivity, though causes of death are similar for individuals with DS whether they live in the community or in an institutional setting (Robertson et al. 2000; Melville et al. 2005; Esbensen et al. 2007; Finlayson et al. 2009; Esbensen 2010).

1.4.4 Healthcare

Given the range of potential health problems which may be associated with DS, it is unsurprising that health screening across the lifespan is recommended (Van Allen et al. 1999; Smith 2001; Roizen & Patterson 2003; Charleton et al. 2010; Bull 2011). However, whilst frequent screening of children is commonplace, less vigilance may be paid in adulthood, and the transition from paediatric care to adult services may not be straightforward (Hallum 1995; Pueschel 1996; Olsen & Swigonski 2004; Schrander-Stumpel et al. 2007). Specialist multidisciplinary services for adults with DS may be beneficial, but few exist (Chicoine et al. 1994; Schrander-Stumpel et al. 2007).

People with ID of all causes, including DS, face health inequalities and barriers to using health services (Cooper et al. 2004). There is evidence that individuals with DS

do not or cannot access adequate healthcare. A study of 151 individuals with ID, including 34 with DS, found that, whilst all participants with DS had seen a GP at least once within the past year, only 38% of individuals with DS had adequate contact with their GP, defined as at a minimum of 4 visits (Howells 1986). The benefits of a nurse-led structured health screening programme in people with ID, in which 28% of both the intervention and control groups had DS, were demonstrated by Cooper et al (Cooper et al. 2006). After 1 year, individuals who underwent the 4 hour screening process had significantly more new health needs detected and treated, as well as higher levels of health promotion and monitoring needs met than individuals who received standard care, despite similar underlying health surveillance requirements in both groups.

Some of the lack of screening in adults with DS may be related to "diagnostic overshadowing" (Reiss et al. 1982). Although the term was originally used to describe the under-diagnosis of mental health problems in individuals with ID, the concept can be related to a number of health issues faced by people with DS which may go unnoticed or ignored due to the misapprehension that they are "just part of the condition". Many individuals with DS and other forms of ID will have a condition diagnosed but not receive treatment due to the mistaken belief of health and social care professionals that they cannot or should not be treated. Most, if not all, conditions associated with DS can be corrected or ameliorated, and an underlying diagnosis of DS should not preclude treatment in the majority of cases.

1.4.5 Advocacy

Charitable organisations play an important part in supporting and advocating for people with DS and their families. Such charities – including, in the UK, Down's Syndrome Scotland, the Down's Syndrome Association and the Down's Heart Group – play a vital role in educating individuals, families, professionals and the general public, promoting inclusion for people with DS and influencing policy at a local and national level. Peer support for individuals with DS and their families can have positive benefits (Mann 1999; Olsen & Swigonski 2004).

In the UK, the Down's Syndrome Association (DSA), a national charity supporting people with DS and their families and carers, developed a Health Book for adults with DS (Down's Syndrome Association 2014). This is provided free of charge in printed form for DSA members, as well as being available as a free electronic download for others. This easy-read book is designed to encourage adults with DS to take ownership of their own health and to see their general practitioner (GP) for annual health screening. The book contains a checklist of areas which should be screened, and supplementary information on DS-related health topics is provided online for GPs. This may help adults with DS access regular health screening and address some of the health inequalities which individuals with DS face (Cooper et al. 2004).

1.5 Conclusion

Although arising from broadly the same genetic abnormality, DS is a complex and wide-ranging disorder, with a broad spectrum of cognitive, health and social effects. Despite the wide range of known comorbidities, services for adults with DS are lacking. As life expectancy continues to rise towards that of the typically-developing population and more individuals with DS reach their elder years, further research into the health and well-being of adults with DS, as well as the underlying aetiology and natural history of DS, is required to ensure that they receive the care and support they require and deserve to maintain quality of life across the lifespan.

Chapter 2: Obstructive sleep apnoea/hypopnoea syndrome: an overview

Sleep-disordered breathing (SDB) is an umbrella term for a spectrum of sleep-related breathing disorders related to narrowing and obstruction of the upper airway. Although arising from similar aetiology, there is a continuum of severity, from primary snoring to severe obstructive sleep apnoea/hypopnoea syndrome (OSAHS), a disorder which can impact significantly on morbidity and mortality. This chapter provides an overview of SDB, focussing on the underlying mechanisms, risk factors, symptoms and consequences of OSAHS.

2.1 The spectrum of sleep-disordered breathing

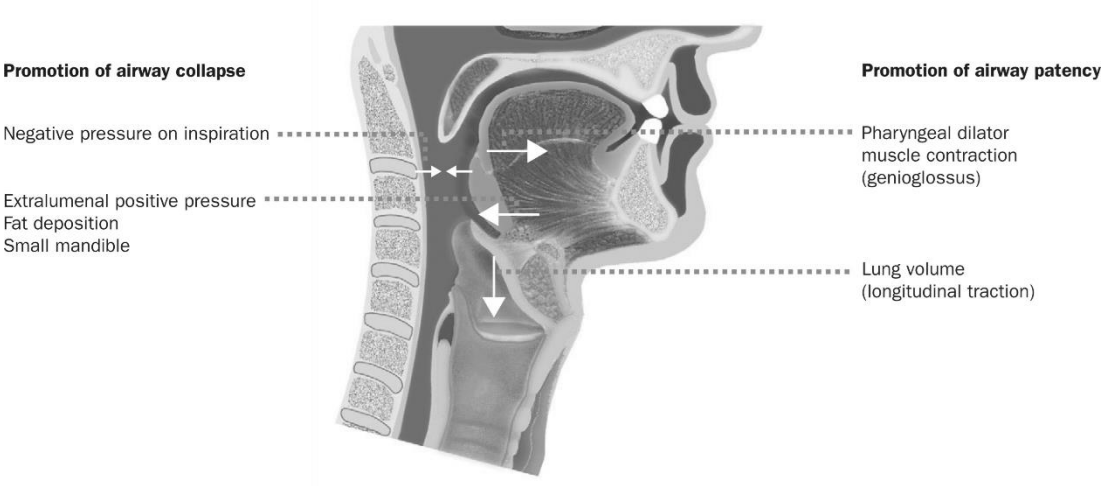
During normal, awake breathing, inspiration is associated with a reduction in pressure within the pharynx, making it susceptible to closure, with an open airway maintained by the action of the pharyngeal muscles. During sleep, a number of factors affect the patency of the upper airway; these are summarised Figure 7 (Malhotra & White 2002). As one falls asleep, skeletal muscles relax, resulting in an overall reduction in muscle tone, reaching total relaxation or atonia in rapid eye movement sleep (REM or stage R). This reduced muscle tone (particularly in the muscles of the pharynx and tongue), alongside the effects of gravity when recumbent, leads to narrowing of the upper airway and an increase in susceptibility to airway collapse during inspiration. Additional factors, such as fat deposits around the neck, the use of sedative medication or alcohol and comorbid conditions affecting muscle tone, can exacerbate this effect, leading to closure of the airway and obstruction of breathing. Limitation of the pharyngeal space due to craniofacial abnormalities or adenotonsillar hypertrophy can also play a part in airway obstruction during sleep. The pathophysiological mechanisms of SDB are discussed in further detail in Section 2.2 below.

2.1.1 Obstructive sleep apnoea (OSA)

OSA is a condition characterised by repeated cycles of pauses in and resumption of breathing. Reduction in breathing due to partial obstruction is known as a

hypopnoea, and complete airway obstruction as an obstructive apnoea. Apnoeas and hypopnoeas are often associated with oxygen desaturation and arousals from sleep, leading to sleep fragmentation. Changes in breathing and other physiological parameters during sleep and wake can be studied objectively using a number of techniques, with internationally-recognised practice parameters and diagnostic criteria used worldwide – these are discussed further in Section 2.6.4.1. An apnoea/hypopnoea index (AHI) of ≥5 events per hour of sleep is generally accepted as diagnostic of OSA in adults, and can be further categorised as mild (AHI 5-14.9), moderate (AHI 15-29.9) or severe (AHI ≥30) (Scottish Intercollegiate Guidelines Network 2003; Epstein et al. 2009).

Figure 7: Factors contributing to maintenance and obstruction of the upper airway in sleep-disordered breathing. Reprinted from The Lancet, Vol. 360, Malhotra A and White DP, Obstructive sleep apnoea, Pages No. 237-45, Copyright (2002), with permission from Elsevier.



2.1.2 Obstructive sleep apnoea/hypopnea syndrome (OSAHS)

The term OSAHS is used when OSA results in significant diurnal symptoms. Many individuals may demonstrate OSA during objective testing, but there is evidence that only those with symptoms benefit from treatment (Barbé 2001). Current guidelines recommend treatment only in symptomatic individuals meeting the criteria for

moderate to severe OSAHS (Loube 1999; Scottish Intercollegiate Guidelines Network 2003; Epstein et al. 2009), although studies have demonstrated improvements in sleepiness, mood and daytime function in symptomatic individuals with mild OSAHS (Engleman et al. 1997; Engleman et al. 1999; Marshall 2005).

2.1.3 Primary snoring

Snoring in the absence of apnoea/hypopnoea is known as primary snoring. While snoring is a commonly associated with OSAHS, not every snorer has OSAHS and not every individual with OSAHS snores (Bearpark et al. 1995). Although most often a complaint of the bed partner rather than the snorer themselves (Hoffstein et al. 1994), snoring has been associated with an increased risk of all-cause mortality in its own right (Rich et al. 2011). Investigation to rule out OSA prior to treatment of primary snoring is warranted.

2.1.4 Upper airways resistance syndrome (UARS)

Narrowing of the airways which causes sleep fragmentation and symptoms such as excessive daytime sleepiness, but does not result in apnoea or hypopnoea *per se*, is known as upper airway resistance syndrome (UARS). There are conflicting views on whether this merits the label of a distinct syndrome, or whether it can be thought of as sub-clinical or pre-clinical OSAHS (Guilleminault 1993; Rees et al. 2000; Velamuri 2006; Pépin et al. 2012).

2.1.5 Central sleep apnoea

Although this overview focuses on obstructive breathing problems, it should be noted that SDB can also be central in origin. In central apnoea, cessation of airflow results from cessation of effort, due to the brain failing to trigger breathing (Eckert et al. 2007). This is more common in young children with an immature chemoreceptor response and usually diminishes with age, but central apnoea may be seen in older children and adults with brain injury, neurological abnormalities, or genetic conditions such as central congenital hypoventilation syndrome (Urquhart 2013). Central apnoea can also be related to obesity hypoventilation (Eckert et al. 2007). Central apnoea, and particularly a pathological breathing pattern known as Cheyne-

Stokes respiration, is commonly found in individuals with congestive heart failure (Lieber & Mohsenin 1991; Naughton 1998).

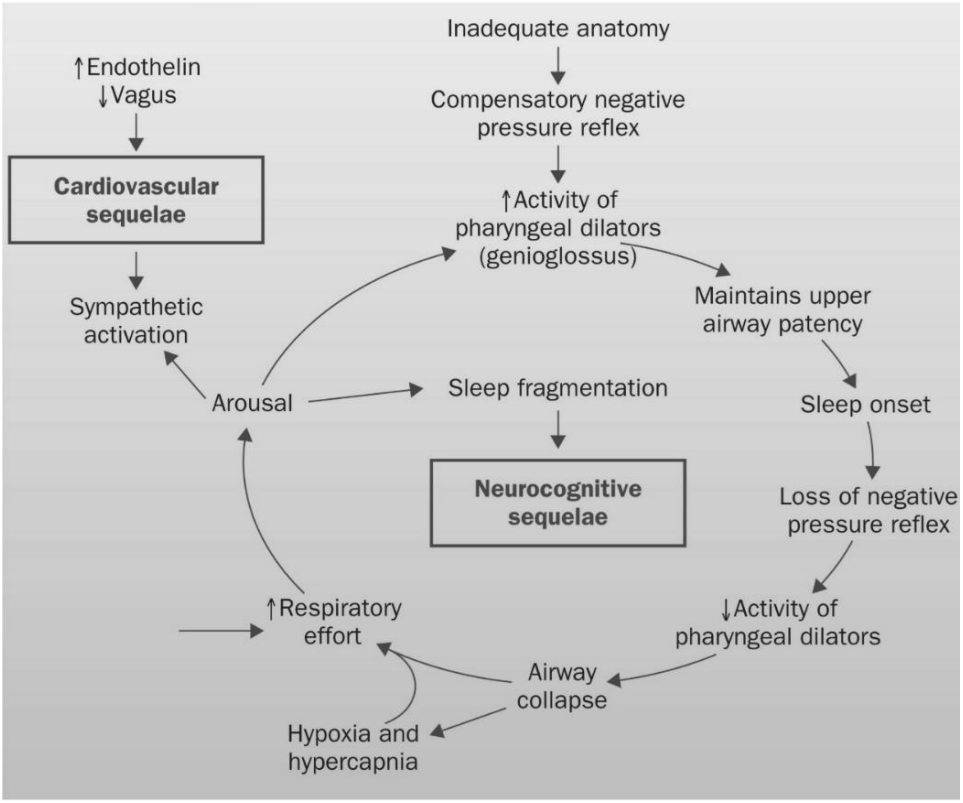
2.2 Pathophysiological mechanism of OSAHS

The pharynx is composed, essentially, of a flexible tube surrounded by muscle and soft tissue, and is, therefore, susceptible to collapse. As detailed in Figure 7, a number of factors are involved in balancing maintenance and closure of the pharyngeal airway during sleep (Malhotra & White 2002). The pathophysiological mechanism of OSAHS has been the subject of a number of excellent reviews (Douglas & Polo 1994; Malhotra & White 2002; Patil et al. 2007; Horner 2008; Eckert & Malhotra 2008), and a summary of these is given here.

Collapsibility of the upper airway varies between individuals, and is a determinant of pressure and resistance. Critical pressure, or P_{CRIT}, is the point at which airflow ceases and the airway collapses. The narrower the airway, the more susceptible it is to collapse, and the higher the $P_{CRIT.}$ However, the upper airway is particularly narrow at the point where the soft palate and tongue are in alignment, and so is vulnerable to obstruction during sleep. A number of anatomical factors, including fat deposition, craniofacial structure, retrognathia and adenotonsillar hypertrophy, contribute to further narrowing of the airway, and sleep (particularly REM sleep), alcohol and sedative drugs inhibit the action of the pharyngeal dilator muscles. These combined factors result in partial (hypopnoea) or complete (apnoea) obstruction of the airway.

Apnoea or hypopnoea leads to both reflex stimulation of the pharyngeal dilator muscles, and to an increase in respiratory effort related to chemoreceptor response to hypoxia/hypercapnia. The increase in respiratory effort results in cortical arousal, further stimulating the activity of the dilator muscles and restoring a patent airway. However, sleep onset post-arousal leads to narrowing of the airway via the mechanisms described above, and the characteristic cycle of repeated obstruction and resumption of breathing of SDB continues – see Figure 8 (Malhotra & White 2002).

Figure 8: Mechanisms of neurocognitive and cardiovascular sequelae of OSAHS. Reprinted from The Lancet, Vol. 360, Malhotra A and White DP, Obstructive sleep apnoea, Pages No. 237-45, Copyright (2002), with permission from Elsevier.



2.3 Epidemiology of OSAHS

A number of studies have assessed prevalence of OSAHS in the adult population using subjective and objective measures (Young et al. 1993; Davies & Stradling 1996; Punjabi 2008; Fuhrman et al. 2012). Although variation is noted between studies due to population and methodological differences, it is generally accepted that SDB affects around 20% of the general population and the prevalence of OSAHS is around 2% in women and 4% in men, based on a middle-aged populations (Jennum & Riha 2009). This estimate is mainly based on objective data from the Wisconsin Sleep Cohort Study, a large longitudinal study (Young et al. 1993) in the USA; a recent follow-up study by the same group reported an increased prevalence of 10-17% in men and 3-9% in women, though this is yet to be replicated in other populations (Peppard et al. 2013). OSAHS affects up to 6% of the paediatric

population (Marcus et al. 2012), with a peak in prevalence at age 2-8 years (Tan et al. 2013).

2.3.1 Risk factors

2.3.1.1 Age

In adults, OSAHS prevalence increases with age, with one study demonstrating an odds ratio of 2.2 for every 10-year increase in age (Duran et al. 2001). A large study in the USA found that in men the prevalence of OSAHS increased with age, peaking in middle-age, though the severity decreased when controlling for BMI (Bixler et al. 1998). A further study from the Wisconsin Sleep Cohort found that, whilst the risk of SDB increased with age, the association between sleepiness and SDB decreased, suggesting that sleepiness may not be the most important symptom in older adults with OSAHS, though this association was again observed only in men (Morrell et al. 2012). Prevalence of OSAHS appears to plateau after the age of 60 years (Duran et al. 2001). The age-related increase in OSAHS is related to a number of features of the normal ageing process including deposition of adipose tissue, diminishing muscle tone, changes to the pharyngeal anatomy and physiology and, in women, menopause (Redline et al. 1994; Martin et al. 1997; Malhotra et al. 2006).

2.3.1.2 Gender

OSAHS occurs more frequently in men than women, with a ratio in the range of 2:1 to 8:1 reported in the literature (Punjabi 2008). A community-based random sample study in Sweden found that 20% of females aged 20-70 years had moderate OSA (Franklin et al. 2013). Studies suggest that men and women may differ not only in the symptoms of OSAHS which they experience, but also in the way in which these symptoms are perceived and reported by their spouse or partner (Kingshott et al. 1995; Punjabi 2008). There is a four-fold increase in the prevalence of OSAHS post-menopause, and hormone replacement therapy is associated with a reduced prevalence of OSAHS (Redline et al. 1994; Bixler et al. 2001; Shahar et al. 2012).

2.3.1.3 Ethnicity

Variations in OSAHS prevalence with differing ethnicity has been reported in children and adults. However, these differences may be related less to ethnicity *per*

se, but more to factors associated with differing ethnicities, such as craniofacial and upper airway structure, obesity, socioeconomic status, health disparity and environment (Villaneuva et al. 2005; Genta et al. 2008; Yamagishi et al. 2010; Sutherland et al. 2012; Ralls & Grigg-Damberger 2012).

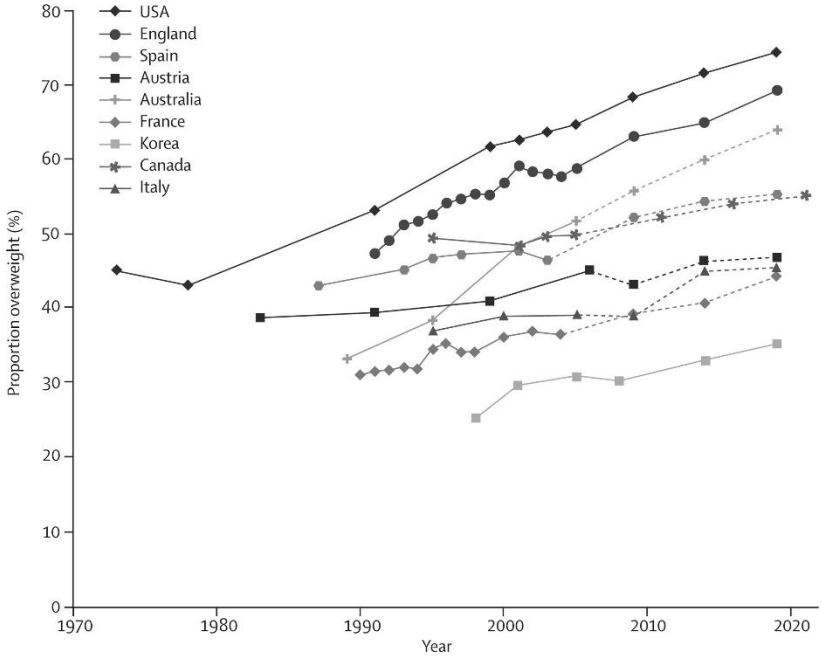
Ethnicity in relation to SDB is further discussed in Chapter 6 in relation to a comparative study of subjective OSAHS prevalence in Scotland and Japan conducted as part of this thesis.

2.3.1.4 BMI and neck circumference

Being overweight or obese remains the biggest risk factor for OSAHS, with over half of all individuals with moderate-to-severe OSAHS having a BMI ≥25 kg/m^2 (Young et al. 2005). Multiple studies around the world have reported an increasing prevalence of OSAHS with increasing body weight, with some studies demonstrating improvement or resolution of OSAHS with surgical or dietary weight loss (Punjabi 2008; Romero-Corral et al. 2010). Given that the prevalence of overweight and obesity is generally rising, both in the UK and worldwide (see Figure 9), this presents a major public health challenge in terms of OSAHS and other comorbidities (Wang et al. 2011).

The relationship between obesity and OSAHS is multifactorial. As well as the mechanical effects of reduced airway size related to fat deposition in the neck and reduced caudal traction related to central obesity, adipose tissue contributes to systemic inflammation and metabolic dysregulation which has been associated with OSAHS and can impact on the neuromuscular control of upper airway patency (Martin et al. 1997; Malhotra & White 2002; Schwartz et al. 2008; Punjabi 2008; Bonsignore et al. 2012).

Figure 9: Global trends in obesity, defined as BMI ≥25. Reprinted from The Lancet, Vol. 378, Wang CY, McPherson K, Marsh T, Gortmaker SL, Brown M, Health and economic burden of the projected obesity trends in the USA and the UK, Pages No. 815-825, Copyright (2011), with permission from Elsevier.



2.3.1.5 Reduced muscle tone

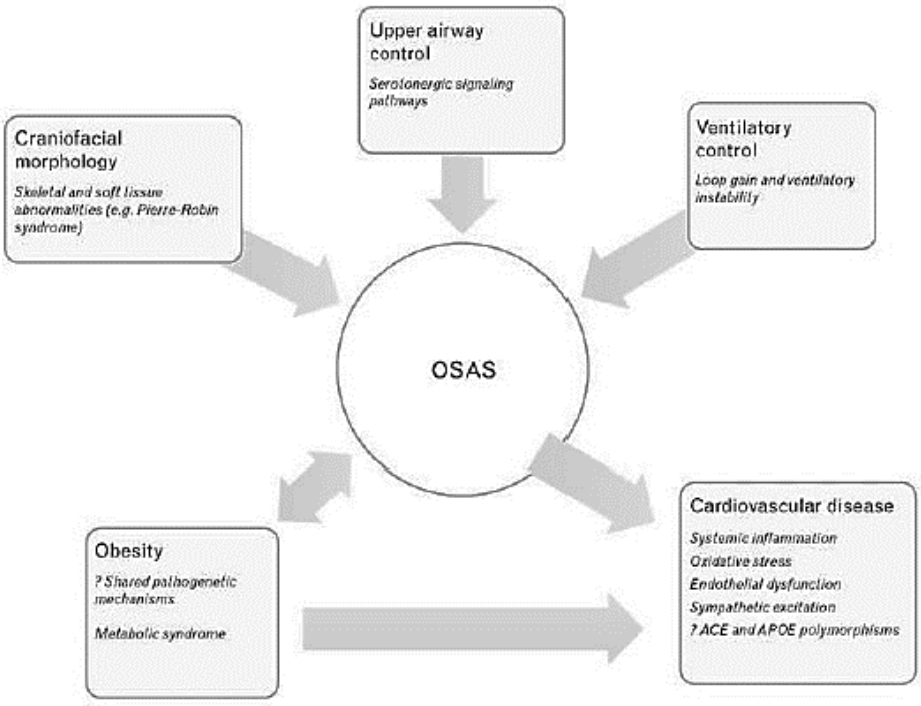
Any disorder or factor which reduces muscle tone will impact on the patency of the upper airway. This includes the intrinsic effects of sleep (particularly REM sleep), fat deposits in the neck, supine posture and normal ageing, as well as extrinsic factors such as the use of alcohol and sedative drugs (Mitler et al. 1988; Martin et al. 1997; Douglas & Polo 1994; Horner 2008). Comorbid medical conditions associated with hypotonia or muscle weakness, such as DS and Duchenne muscular dystrophy, are also associated with an increased risk of OSAHS (Primhak & Kingshott 2012). The links between DS and OSAHS is discussed in detail in Chapter 3 of this thesis.

2.3.1.6 Adenotonsillar hypertrophy

Enlargement of the tonsils and adenoids is the most common cause of OSAHS in children. Adenotonsillectomy is considered the standard first-line treatment for OSAHS in children, and is curative in 75-100% of cases (Schechter 2002). In adults,

large tonsils and adenoids can impact on the pharyngeal space, increasing the risk of airway closure during sleep. Tonsillar size is routinely assessed clinically using the Mallampati or Friedman rating scales (Mallampati et al. 1985; Friedman 2002), with higher scores associated with higher risk of OSAHS (Liistro et al. 2003; Nuckton et al. 2006; Rodrigues et al. 2010).

Figure 10: Intermediate phenotypes and heritable factors in OSAHS. Reprinted from Kent BD, Ryan S and McNicholas WT, The genetics of obstructive sleep apnoea, Current Opinion in Pulmonary Medicine, 2010, 16: 536-542, with permission.



2.3.1.7 Genetics

The hereditary nature of OSAHS has been demonstrated in a number of studies (Redline & Tishler 2000; Riha et al. 2009; Kent et al. 2010), and genetic factors are thought to account for around 40% of the variance in AHI seen in OSAHS (Redline & Tishler 2000). The heritable factors associated with OSAHS and their contribution

to the OSAHS phenotype are summarised in Figure 10 below (Kent et al. 2010), and have been discussed in detail elsewhere in this chapter.

2.3.1.8 Comorbidities

A number of congenital disorders, including neuromuscular and skeletal disorders (e.g. Duchenne muscular dystrophy, scoliosis), craniofacial abnormalities (e.g. Pierre Robin sequence, achondroplasia) and genetic disorders (e.g. DS, Prader-Willi syndrome) can predispose to OSAHS (Primhak & Kingshott 2012). In the context of this thesis, a detailed discussion of the links between DS and OSAHS is provided in Chapter 3.

2.4 The OSAHS phenotype

OSAHS is characterised by a series of nocturnal and diurnal symptoms which are summarised in Table 3 and discussed in further detail below.

2.4.1 Nocturnal symptoms

Snoring and witnessed apnoeas are the most common nocturnal symptoms of OSAHS. The prevalence of these symptoms varies between studies, due to population and methodological differences. However, epidemiological studies suggest that up to 50% of men and 17% of women in the general population snore (Lindberg 2010), rising to up to 100% in those with an AHI ≥15 (Redline et al. 1994). The percentage of individuals snoring on ≥3 nights per week increases with increasing AHI (Young 1996). Witnessed apnoeas rely on spouse or bed partner report, and are reported less often in females than males; witnessed apnoeas were reported by 8% of males and 5% of females in one community-based study, rising to 61% of males and 37% of females with an AHI≥15 (Young 1996). Another study reported witnessed apnoeas in 42% of males and 12% of females with a similar AHI (Redline et al. 1994). In a Danish study, 25% of males and 18% of females with an AHI≥5 were habitual snorers, with witnessed breathing pauses noted by 17% and 13% of males and females respectively (Jennum & Sjøl 1992). A more recent study in France reported witnessed apnoeas in 13% of men and 5% of women in the

general population, with 14% of men and 6% of women snoring almost every night (Fuhrman et al. 2012).

The repeated cycle of apnoea and arousal results in sleep fragmentation, which may manifest as restlessness and unrefreshing sleep. Experimentally-induced sleep fragmentation has been shown to impair daytime function (Martin et al. 1996), and the neurocognitive impact of untreated OSAHS is discussed further in Section 2.5.4 below.

Table 3: Nocturnal and diurnal symptoms of OSAHS.

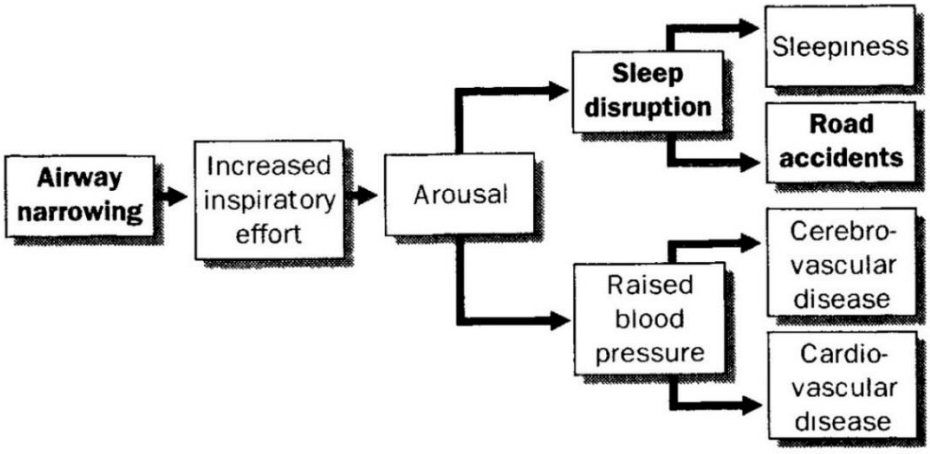
Nocturnal symptoms	**Diurnal symptoms**
Snoring	Excessive daytime somnolence (EDS)
Witnessed apnoeas	Morning headache
Gasping or choking episodes	Dry mouth
Restlessness	Poor concentration/memory
Frequent awakenings	Mood disturbances
Nocturia	Behavioural disturbances

2.4.2 Diurnal symptoms

Excessive daytime sleepiness (EDS) is the most prominent feature of OSAHS, arising from sleep fragmentation due to repeated cycles of arousal during sleep – see Figure 8 above and Figure 11 below. EDS is most commonly measured subjectively using the Epworth Sleepiness Scale (ESS; Johns 1991), which is discussed in detail in Chapter 5, and objectively using the multiple sleep latency test (MSLT; Littner et al. 2005). Individuals with EDS related to OSAHS often report daytime napping or sleep attacks, as well as falling asleep in social and work situations. This can impact negatively on employment, social function and quality of life. Sleepiness when driving may occur, and individuals with EDS are more likely to be involved in road traffic accidents than the general population (Iranzo 2010). Often, the individual themselves is not fully aware of the extent of their sleepiness, and bed partners or

proxies tend to give higher ESS scores than patients themselves (Kingshott et al. 1995; Walter et al. 2002).

Figure 11: Effects of airway narrowing. Reprinted from The Lancet, Vol. 2, Douglas NJ and Polo O, Pathogenesis of obstructive sleep apnoea/hypopnoea syndrome, Issue 8923 Page no. 653–655, Copyright (1994), with permission from Elsevier.



Daytime cognitive function is impaired, with deficits in attention, concentration and memory evident, as well as mood disturbances; again, this is discussed further in Section 2.5.4. Dry mouth and nasal congestion are common, related to mouth breathing in an attempt to overcome airway obstruction. Morning headaches, related to nocturnal hypercapnia, are also frequently reported.

2.5 Consequences of untreated OSAHS

Left untreated, OSAHS is associated with a number of deleterious consequences, leading to increased morbidity and mortality.

2.5.1 All-cause mortality

Untreated OSAHS is associated with increased mortality. A study of over 6,400 individuals participating in the Sleep Heart Health Study in the USA found a

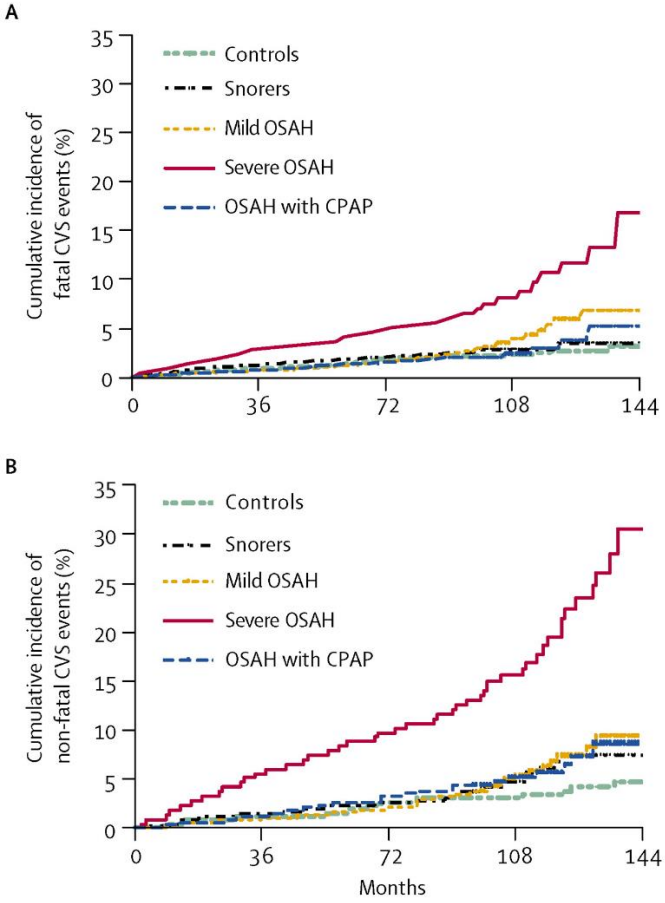
significant association between SDB and all-cause mortality, with hypoxaemia (but not sleep fragmentation) independently associated with mortality (Punjabi et al. 2009). A further large cohort study in Australia, the Busselton Health Study, found that moderate/severe, but not mild, OSA was related to increased risk of all-cause mortality (Marshall et al. 2008). Self-reported witnessed apnoeas were associated with all-cause mortality in the Swedish Obese Subjects study (Marshall et al. 2011).

2.5.2 Cardiovascular effects

OSAHS has been associated with cardiovascular sequelae, including hypertension, ischaemic heart disease, congestive heart failure and stroke (Parati et al. 2013). In a 10-year observational study, Marin et al (Marin et al. 2005) demonstrated that severe OSAHS in men increased the risk of fatal and non-fatal cardiovascular events in comparison with healthy controls, primary snorers, individuals with mild-moderate OSAHS and patients on CPAP by an odds ratio of 3 – see Figure 12. Severe SDB in men aged 40-70 years was associated with mortality due to coronary artery disease in the Sleep Heart Health Study (Punjabi et al. 2009). OSAHS has been shown to be an independent risk factor for pulmonary hypertension, with around 20% in one study developing mild daytime pulmonary hypertension (Alchanatis et al. 2001).

As summarised in Figure 8 and Figure 11, cardiovascular dysfunction in OSAHS is in part related to sympathetic nervous system activation secondary to arousal (Douglas & Polo 1994; Malhotra & White 2002). However, the relationship between OSAHS and cardiovascular morbidity is multifactorial, with intermittent hypoxia, endothelial dysfunction, systemic inflammation and disruption of the renin-angiotensin-aldosterone system all thought to play a role (Parati et al. 2013).

Figure 12: Cumulative percentage of men with new fatal (A) and non-fatal (B) cardiovascular events in each of the five groups studied by Marin et al. Reprinted from The Lancet, Vol. 365, Marin JM, Carrizo SJ, Vicente E, Agusti AGN, Long-term cardiovascular outcomes in men with obstructive sleep apnoea-hypopnoea with or without treatment with continuous positive airway pressure: an observational study, Pages No. 1046–1053, Copyright (2005), with permission from Elsevier.



2.5.3 Endocrine dysfunction

A multitude of studies worldwide have shown an independent association between OSAHS and impaired glucose metabolism, abnormal lipid metabolism and metabolic syndrome (Lam et al. 2010). As mentioned above, a number of mechanisms are thought to be involved in OSAHS and metabolic dysfunction, including sleep fragmentation, intermittent hypoxia, oxidative stress, systemic inflammation, dysregulation of the leptin/ghrelin system and hormonal effects of adipose tissue (Lam et al. 2010).

2.5.4 Neurocognitive sequelae

A meta-analysis by Beebe et al (Beebe et al. 2003) and a more recent meta-review by Bucks et al (Bucks et al. 2013) have described the cognitive deficits commonly observed in individuals with OSAHS and the possible mechanisms underlying these. OSAHS has been associated with a wide range of neurocognitive deficits, encompassing learning, memory, attention, executive function and mood, likely related to the effects of both intermittent hypoxia and sleep fragmentation. Impairment in these areas has clear implications for everyday function and quality of life for people with untreated OSAHS.

A number of brain imaging studies have described changes in brain morphology associated with OSAHS, including reduced volumes in the hippocampus, cerebellum, prefrontal cortex and temporal lobe (Morrell & Glasser 2012). As discussed in Chapter 1, the hippocampus has a role in declarative memory and consolidation of learning, the prefrontal cortex is involved in executive function and working memory and the cerebellum has involvement in visual-motor skills, emotion and affect, although there is some overlap between functions between brain regions.

2.5.4.1 Learning and memory

A relationship between sleep and memory has been well described. In a review of sleep-dependent memory consolidation by Stickgold, it was noted that, in a series of six experimental studies examining the link between sleep and memory, sleep accounted for 69% of the variance in learning/memory task performance, demonstrating a very close correlation between the two (Stickgold 2005). It stands to reason, therefore, that sleep disruption related to OSAHS may be associated with deficits in learning and memory. Memory problems are subjectively reported by more than half of patients with OSAHS (Jennum & Sjøl 1992; Flemons & Reimer 1998).

The meta-analysis by Beebe et al found inconsistent results in terms of memory function in OSAHS, possibly due to methodological differences between studies (Beebe et al. 2003), though a previous meta-analysis noted a moderate effect in memory-related performance scores in adults with OSAHS (Engleman et al. 2000).

A further meta-analysis of studies assessing the effects of OSAHS on episodic memory (Wallace & Bucks 2013)found impairments in verbal and visuospatial, but not visual, memory; the authors proposed that this may be related to dysfunction of the prefrontal cortex. Prefrontal cortex dysfunction secondary to OSAHS has been implicated in a range of adverse effects on daytime function (Beebe & Gozal 2002), and this is discussed further in relation to behaviour below.

2.5.4.2 Attention

Individuals with OSAHS commonly complain of problems with concentration; 23% of adults with OSAHS in a Swedish cohort (Jennum & Sjøl 1992) and 69% in a Canadian study (Flemons & Reimer 1998) reported concentration problems. Objective testing of attention and vigilance in individuals with OSAHS also shows impairment (Engleman et al. 2000; Beebe et al. 2003; Bucks et al. 2013). An Italian study showed that, whilst reaction time was impaired in individuals with OSAHS relative to controls, this was significantly improved after only 15 days on CPAP, which was sustained after 4 months of therapy (Ferini-Strambi et al. 2003).

It has been suggested that individuals with higher IQ have a greater "cognitive reserve", and so are less sensitive to cognitive impairment associated with OSAHS (Alchanatis et al. 2005). When individuals with OSAHS underwent tests of attention and alertness, individuals with a high IQ performed as well as normal-IQ controls, whilst the OSAHS patients with normal IQ showed impairment in comparison with controls. However, after a year of CPAP treatment, both groups performed as well as controls.

2.5.4.3 Executive function

Impaired executive function has been noted in adults with OSAHS in many studies, though recent reviews suggest that the this is neither related to OSAHS severity nor significantly improved with CPAP therapy (Engleman et al. 2000; Bucks et al. 2013). Ferini-Strambi et al demonstrated improvements in tests of executive functioning after 15 days of CPAP, though this did not reach significance after 4 months. Canessa et al examined the link between morphometric changes and cognitive function (Canessa et al. 2011). Reduced volumes in the hippocampus were related to

impaired performance on tests of memory and executive function; after treatment with CPAP, improved performance on these tests was noted, and was associated with increased hippocampal volume. Impaired hippocampal function appears to be related to intermittent hypoxia (Feng et al. 2012). The deficits observed in attention and vigilance in individuals with OSAHS appear to be related to sleep fragmentation more so than hypoxaemia (Engleman et al. 2000; Bucks et al. 2013), and experimentally-induced sleep fragmentation results in similar decrements in attention and vigilance tasks (Martin et al. 1996).

2.5.4.4 Motor skills

Inconsistent effects of OSAHS on motor function skills have been noted (Bucks et al. 2013), though some studies have shown visuo-motor deficits which may be improved by CPAP (Ferini-Strambi et al. 2003; Chen et al. 2012).

2.5.4.5 Depression

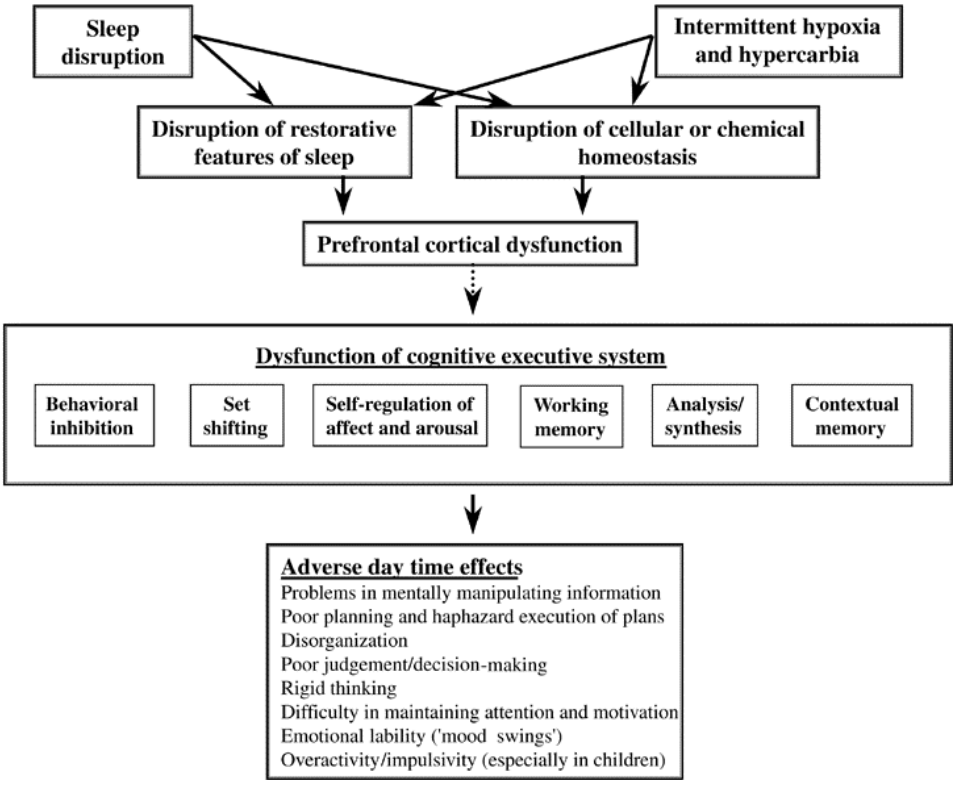
Irritability and low mood are common symptoms of OSAHS, and just one night of sleep fragmentation via experimental methods has been shown to impair mood (Martin et al. 1996). Co-existing depression is frequently observed in individuals with OSAHS, and overlap between the symptoms of both may hinder diagnosis (Harris et al. 2009). In one study in Mexico, 57% of individuals with AHI≥5 had symptoms of anxiety and/or depression (Reyes-Zuniga 2012) and, in Australia, 32-53% of individuals referred for investigation of snoring or OSAHS had symptoms of or were receiving treatment for depression (Douglas et al. 2013)..

2.5.4.6 Behavioural and emotional disturbance

Particularly in children, sleepiness related to SDB can manifest as hyperactivity or behavioural or emotional disturbance, rather than overt sleepiness (Gozal 2000), with children with symptoms of SDB more likely to exhibit aggression and bullying behaviours (O'Brien et al. 2011). As discussed above, problems with low mood and depression are apparent in adults with OSAHS. Beebe and Gozal proposed a model whereby OSAHS lead to behavioural and emotional disturbance in both children and adults due to the impact of sleep fragmentation and intermittent hypoxia on the prefrontal cortex; this is summarised in Figure 13 below (Beebe & Gozal 2002).

Prefrontal dysfunction secondary to OSAHS may explain a number of the neurocognitive deficits observed in individuals with untreated OSAHS.

Figure 13: Beebe and Gozal's prefrontal model. Reprinted from Beebe DW and Gozal D (2002), Obstructive sleep apnea and the prefrontal cortex: towards a comprehensive model linking nocturnal upper airway obstruction to daytime cognitive and behavioral deficits. Journal of Sleep Research, 11: 1–16. With permission, Wiley.



2.5.4.7 Dementia

Despite the clear evidence of a link between cognitive impairment and OSAHS, few studies have formally evaluated the role of OSAHS in Alzheimer disease or vascular dementia. However, a review of the evidence suggests that a causal link between OSAHS and dementia may exist (Bliwise 2013). A prospective study of nearly 300 older women without dementia found that those with SDB were at higher risk of developing mild cognitive impairment or dementia than non-SDB controls, though no associations with sleep fragmentation or hypoxia were noted (Yaffe et al. 2011).

A recent retrospective study of over 1400 patients in Taiwan suggests that individuals with OSAHS have a 1.7 times greater risk of developing dementia within 5 years of diagnosis when compared to age- and gender-matched controls without OSAHS (Chang et al. 2013). It has been suggested the brains of older people may be more sensitive to intermittent hypoxia associated with OSAHS, which may accelerate cognitive decline in this group (Morrell et al. 2012), potentially predisposing to the onset of dementia. However, further investigation in this area is required.

2.6 Diagnosis of OSAHS

This section summarises the range of subjective and objective methods for assessment and diagnosis of OSAHS.

2.6.1 Clinical history

Although taking a good clinical history is a vital part of the diagnostic process, clinical history and physical examination alone has been shown to be a poor indicator of OSAHS (Viner 1991) and further subjective and objective screening is usually required.

2.6.2 Screening questionnaires

A number of screening questionnaires have been validated in the assessment of OSAHS. The ESS is a widely-used measure of sleepiness over recent times (Johns 1991). The Stanford Sleepiness Scale (SSS) provides a point-in-time assessment of sleepiness (Hoddes et al. 1973), making it useful for repeated measures across a given period, for example prior to each nap of an MSLT. The Karolinska Sleepiness Scale offers a similar, Likert-type scale (Åkerstedt & Gillberg 1990). Other questionnaires have been developed to assess a wider range of OSAHS symptoms beyond sleepiness alone. One example, the STOP-BANG questionnaire, was originally developed to screen for possible OSAHS prior to anaesthesia, and has since been found to be useful in a more general sleep clinic setting (Chung et al. 2008; Vasu et al. 2010; Chung et al. 2012). A review of the full range of screening

questionnaires available is outwith the scope of this thesis; however, the questionnaires used during the studies described herein are described in the relevant Chapters.

2.6.3 Objective testing

Although screening questionnaires can be useful, objective measurement of sleep by sleep study is required to quantify the underlying level of SDB. A variety of different types of sleep study device are available, recording single or multiple channels of physiological data during sleep and wake overnight and during the day, at home or in a sleep laboratory setting. The American Sleep Disorders Association (ASDA) defined four levels of portable device based on the number of channels and quality of data recorded (Ferber et al. 1994).

2.6.3.1 Level I Devices

Level I sleep studies, or standard polysomnography (PSG), record a minimum of seven channels of data, including EEG, electrooculogram (EOG), electromyogram (EMG), electrocardiogram (ECG), airflow, respiratory effort, oxygen saturation and body position (Ferber et al. 1994). Since the ASDA guidance was written, the use of video recording as part of the PSG study is now commonplace. This combination of channels allows the definitive staging of sleep as well as monitoring of respiration, oxygenation and body movements associated with SDB and other sleep disorders. For this reason, PSG is considered the reference-standard test for diagnosis of OSAHS (Penzel et al. 2010). Level I PSG must be fully attended overnight by an experienced technologist, and international guidelines and technical specifications for the set-up recording and scoring of PSG were published by the American Academy of Sleep Medicine in 2007 (Iber et al. 2007); these are discussed further in Section 2.6.4 below. Practice parameters for the use of PSG have also been published (Kushida et al. 2005). Due to the requirement for costly specialist equipment, an in-patient bed, and skilled staff in attendance overnight and to score the study, level I PSG is the most expensive sleep study, and this may limit its availability. The SIGN guidelines for OSAHS state that PSG is not required for diagnosis of OSAHS in the majority of cases, but should be available in tertiary centres for the assessment of

more complex or equivocal cases (Scottish Intercollegiate Guidelines Network 2003)..

2.6.3.2 Level II Devices

Ambulatory PSG is described as a level II device. This type of device records the same channels as level I PSG, but this is unattended and can be carried out in the patient's own home. Although the cost of an in-patient bed is negated, specialist equipment and staff are still required to set up the equipment during an outpatient or home visit and to score the results. The risk of signal loss is high due to the unattended nature of the study. For these reasons, ambulatory PSG is not commonly used clinically. However, most modern PSG systems can now be used in both in- and outpatient settings, and some systems will allow the recording of digital video at home.

2.6.3.3 Level III Devices

Level III devices, known as modified portable sleep apnoea testing devices, limited studies, cardiorespiratory studies or polygraphy, are frequently used, and practice parameters have been published (Collop et al. 2007). By definition, a level III device must have a minimum of four channels, including two channels of respiratory effort or respiratory effort and airflow, heart rate or ECG and oxygen saturation (Ferber et al. 1994). An important difference between these devices and level I or II PSG is that the channels required for sleep staging are absent, and so diagnosis of OSAHS is based on time in bed, rather than total sleep time and, additionally, there is no valid measure of EEG arousal – this can result in a dilution of the AHI by around 20% (Hedner et al. 2011), and this is discussed further in Chapter 7. Level III devices require less specialist knowledge to set up, and patients can be quickly and easily instructed in their use, allowing collection of the equipment to set up themselves at home. Again, some systems allow the integration of video recording. Although signal loss is a risk, patients can easily reattach sensors if they come off, more so than with level I or II PSG. Many individuals report a more representative night's sleep at home in their own bed rather than in the hospital environment. The combination of an unattended outpatient study, less expensive equipment and far quicker and easier scoring mean that polygraphy can offer significant cost savings, in

the region of 42-50%, over level I or II studies (Dingli et al. 2003; Juan F. Masa et al. 2011). Level III polygraphy is indicated as the first-line diagnostic test for individuals with a high clinical suspicion of OSAHS and, given its high sensitivity and specificity for detection of OSAHS, can be used to exclude as well as diagnose the condition, although PSG may still be required if results are equivocal (Ferber et al. 1994; Scottish Intercollegiate Guidelines Network 2003; Collop et al. 2007; Penzel et al. 2010). Further discussion of level III polygraphy in the context of this thesis can be found in Chapter 7.

2.6.3.4 Level IV Devices

The most basic sleep study devices record only one or two channels of data, the most commonly used level IV device being pulse oximetry. Oximetry has the benefit of being portable, easy to use and relatively cheap, allowing quick-turnaround, high-volume screening, and many clinical sleep services will use this as a first-line test to screen all new patients. However, there are significant limitations. A single (or dual) channel recording is at very high risk of signal loss – if one channel is lost or affected by artefact, the entire study is invalidated, which may result in the requirement for a repeat study, incurring additional time and cost. Level IV devices do not record EEG, and so no true measure of sleep is recorded, only time in bed. Further, a number of validation studies have shown that, whilst sensitivity for diagnosis of OSAHS is high, specificity is generally low (Ferber et al. 1994), and so current guidelines recommend that oximetry cannot be used to rule out OSAHS, with a "negative" study considered equivocal and further testing with a higher level sleep study device required (Scottish Intercollegiate Guidelines Network 2003).

2.6.4 Scoring and interpretation of sleep studies

2.6.4.1 Scoring criteria and guidelines

In 1968, Rechtshaffen and Kales introduced the first classification of sleep stages based on electrophysiological measures (Rechtschaffen & Kales 1968). These "R&K rules" remained the gold-standard guidelines for sleep staging until 2007, when the American Academy of Sleep Medicine (AASM) introduced its Manual for the Scoring of Sleep and Associated Events (Iber et al. 2007). Unlike the R&K rules, this comprehensive manual, for the first time, incorporated guidelines for scoring EEG

arousals, respiratory events and movement events alongside sleep staging. The Manual is a dynamic document, having been further updated a number of times since Version 1, with planned updates on a twice-yearly basis. However, although the Manual was generally seen as a step forward in the standardisation of practice in sleep medicine, changes to the rules have often been controversial, with studies suggesting differences in diagnostic outcomes based on different versions of the guidelines and between recommended and acceptable alternative rules within the Manual (Ruehland et al. 2009).

In adults, The American Academy of Sleep Medicine (AASM) Manual for the Scoring of Sleep and Associated Events Version 1 (Iber et al. 2007) defines a hypopnoea as a ≥30% reduction in a valid measure of airflow of at least 10s duration, associated with dip in SpO2 of ≥3% and/or an EEG arousal. An obstructive apnoea is defined as a ≥90% reduction in airflow for a minimum duration of 10s, with no arousal or desaturation requirement. Further discussion of the scoring rules and recording equipment can be found in the Methods section of Chapter 7 of this thesis.

2.6.4.2 Diagnostic thresholds

The International Classification of Sleep Disorders 2nd edition defines the diagnostic threshold for OSAHS as an AHI or respiratory disturbance index (RDI) ≥5 events per hour of sleep in association with symptoms including sleepiness, hypersomnolence, insomnia, arousals with feeling of asphyxiation/ suffocation, snoring or witnessed apnoeas, where the disorder cannot be attributed to other conditions, use of medicines or other substances (American Academy of Sleep Medicine 2005). Both the ICSD-2 and SIGN guidelines classify the severity of OSAHS as: mild: 5-15 events per hour; moderate: 15-30 events per hour; and severe: more than 30 events per hour (Scottish Intercollegiate Guidelines Network 2003; American Academy of Sleep Medicine 2005). SIGN recommends treatment of all symptomatic patients with moderate-to-severe OSAHS. It should, however, be noted that differing thresholds are used between studies in the literature, which may account for some of the differences observed between them.

2.7 Treatment of OSAHS

A range of treatment options are available for SDB and OSAHS, and are briefly described here.

2.7.1 Continuous positive airway pressure

Continuous positive airway pressure therapy (CPAP) is recognised as the first-line treatment for OSAHS in adults, and, since its introduction in 1981, has changed the lives of millions of people world-wide.

2.7.1.1 History and mechanism

CPAP was invented by Professor Colin Sullivan and introduced via a landmark paper in 1981(Sullivan et al. 1981). A simple, non-invasive treatment, CPAP involves delivering pressurised room air via a mask positioned over the nose (or nose and mouth) to reverse the negative intrathoracic pressure generated during an apnoea by providing pneumatic splinting of the airway, as shown in Figure 14. Despite its simplicity, Sullivan and colleagues demonstrated an instant and dramatic improvement in oxygen saturation and AHI in a cohort of five patients, aged 13 to 55, with severe OSAHS. An example is shown in Figure 15, where the saturation trace of one individual who had previously shown repeated desaturations into the 80%s was normalised by the application of CPAP.

2.7.1.2 Benefits

Since this original landmark study, the efficacy of CPAP has been demonstrated in a range of trials, including randomised controlled trials using placebo or sham CPAP. These trials have shown CPAP to be effective in ameliorating many of the consequences discussed above, including EDS, cognitive dysfunction and metabolic and cardiovascular outcomes (Engleman et al. 1994; McFadyen et al. 2001; Engleman et al. 2002; Patel et al. 2003; Ferini-Strambi et al. 2003; Marin et al. 2005; Weaver et al. 2007; West et al. 2007; Coughlin et al. 2007; Antic et al. 2011; Kylstra et al. 2013).

All-cause mortality is improved by the use of CPAP; a study of 444 individuals with SAHS over 10 years found that those with untreated OSAHS had significantly higher

mortality than those using CPAP, with use of CPAP therapy reducing the risk of all-cause mortality to a similar level as the general, non-OSAHS, population (Marti et al. 2002). Further retrospective reviews have continued to support these observations (Marin et al. 2005).

Figure 14: Mechanism of upper airway occlusion and its prevention by CPAP. During wake, muscle tone prevents airway collapse during inspiration (top panel); during sleep, the tongue and soft palate collapse due to negative intrathoracic pressure (middle panel). CPAP provides a pneumatic splint, keeping the airway open (lower panel). Reprinted from The Lancet, Vol. 317, Issue 8225, Sullivan CE, Berthon-Jones M, Issa FG, Eves L, Reversal of obstructive sleep apnoea by continuous positive airway pressure applied through the nares, Pages no. 862-865, Copyright (1981), with permission from Elsevier.

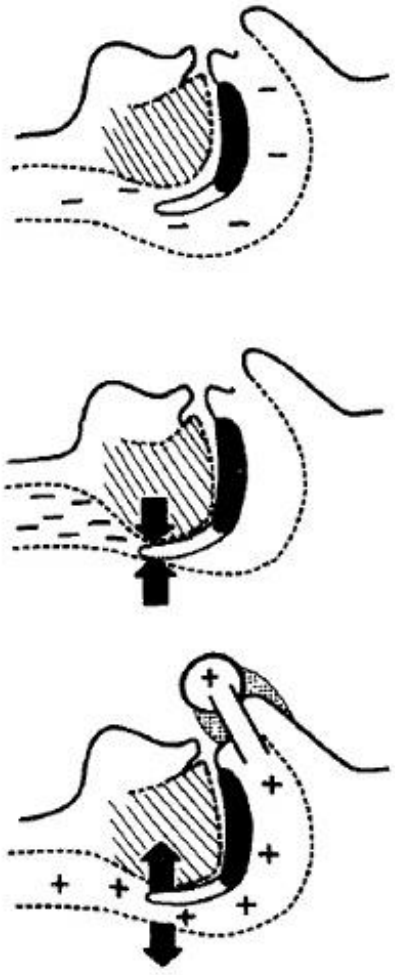
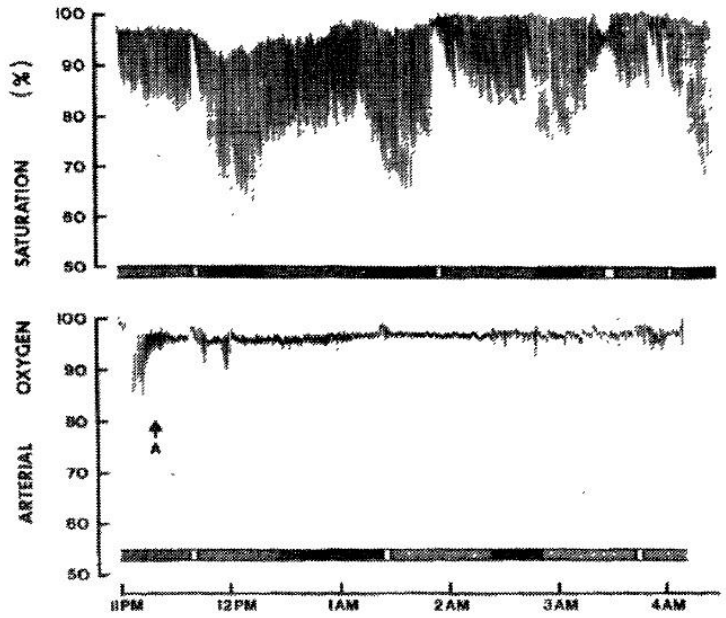


Figure 15: Normalisation of oxygen saturation during sleep after one night of CPAP therapy. A single patient's control night (upper panel) and CPAP night (lower panel) are shown. CPAP at 7.0cmH_2O was applied at arrow A and sustained for the remainder of the night. Reprinted from The Lancet, Vol. 317, Issue 8225, Sullivan CE, Berthon-Jones M, Issa FG, Eves L, Reversal of obstructive sleep apnoea by continuous positive airway pressure applied through the nares, Pages no. 862-865, Copyright (1981), with permission from Elsevier.



2.7.1.3 Side-effects and compliance issues

Although CPAP is simple, non-invasive and effective, it does have some side effects. A proportion of users will struggle to tolerate CPAP, and many will discontinue the therapy. There is evidence that many make the decision to continue or quit CPAP within the first 1-2 weeks (Hoy et al. 1999; Ye et al. 2012; Balachandran et al. 2013), and intensive education and support has been shown to improve compliance in the longer term (Hoy et al. 1999). Psychological and behavioural interventions may be effective in improving CPAP compliance (Engleman & Wild 2003). The choice of CPAP interface is also important (Parthasarathy 2008; Borel et al. 2013).

Side effects can be a barrier to compliance with CPAP; common side effects of CPAP include nasal dryness or congestion, skin irritation or discomfort related to the

mask interface and aerophagia, which can result in bloating and flatulence, and claustrophobia (H. M. Engleman et al. 1994; Stepnowsky et al. 2002; Chasens et al. 2005; Weaver & Grunstein 2008). Dryness and congestion can be easily remedied by the addition of heated humidification, though this does not necessarily improve compliance with treatment (Massie et al. 1999; Martins de Araújo 2000; Neill et al. 2003; Worsnop et al. 2010; Koutsourelakis et al. 2010). Other factors affecting compliance include age, gender, ethnicity, low socioeconomic status and psychological factors (Engleman et al. 1994; Weaver & Grunstein 2008; Olsen et al. 2008; Simon-Tuval et al. 2009; Ye et al. 2012). CPAP may be ineffective or minimally effective in individuals who are asymptomatic or have only mild OSAHS (Engleman et al. 1997; Barbé 2001)

2.7.1.4 Guidelines

CPAP is recommended as the first-line treatment for OSAHS in adults by a number of guidelines and reports, including those published by SIGN, National Institute for Clinical Excellence and the AASM (Scottish Intercollegiate Guidelines Network 2003; National Institute for Clinical Excellence 2008; Epstein et al. 2009).

2.7.2 Non-CPAP therapies

Although treatments other than CPAP are available, there is a paucity of evidence to support their use as a standalone treatment for OSAHS in most cases and CPAP remains the first-line treatment for most. However, these may be useful as an adjunct to CPAP therapy, or as a first-line treatment for sub-OSAHS SDB. The use of alternative therapies may also be indicated in the event of inability to tolerate CPAP.

2.7.2.1 Weight reduction

In individuals who are overweight, weight loss can be effective in reducing the severity of OSAHS, though this can be difficult to achieve and maintain. In a 3-way randomised trial of CPAP versus mandibular advancement device (see 2.7.2.4 below) versus weight loss, weight loss was associated with a reduction in AHI, but did not significantly improve OSAHS, daytime sleepiness or quality of life (Lam et al. 2007). A recent European Respiratory Society Task Force concluded that the available evidence for weight loss as a standalone treatment for OSAHS was

inconsistent (Randerath et al. 2011). However, given the health and economic benefits of weight loss generally (Oster et al. 1999), all overweight and obese individuals with OSAHS should be advised to lose weight, irrespective of other treatment for OSAHS.

2.7.2.2 Pharmacological intervention

Although a number of pharmacological treatments for OSAHS have been proposed, including theophylline, acetazolamide, selective serotonin reuptake inhibitors, cholinergic agents and nocturnal oxygen, no single medication has been consistently effective in treating OSAHS (Hedner & Zou 2010; Randerath et al. 2011).

2.7.2.3 Surgical intervention

A number of surgical options for treatment of OSAHS are available. Removal of the uvula and soft palate using laser, radiofrequency ablation or by uvulopalatopharyngoplasty (UPPP) are not recommended as a sole treatment for OSAHS and, indeed, can make future CPAP treatment problematic (Mortimore et al. 1996; Han et al. 2006). A less invasive technique, known as Pillar implants, uses short fibre rods which are inserted into the soft palate under local anaesthetic. This stiffens the soft palate and has been shown to be effective in individuals with primary snoring and mild/moderate OSAHS, and can be used in conjunction with CPAP (Maurer et al. 2005; Bertoletti et al. 2009).

Maxillofacial surgery to reposition the upper and/or lower jaw and thereby increase the pharyngeal airspace has been shown to be effective in individuals where craniofacial abnormality is the primary cause of OSAHS (Mehra & Wolford 2000), though the invasive nature of this procedure makes it less desirable as a standard treatment for the majority of OSAHS patients.

Surgical weight loss via bariatric surgery is a treatment option in super-obese patients. However, long-term follow-up data on the effect of bariatric surgery on OSAHS in these patients is limited, and perioperative complications appear common (Chang et al. 2010). Further studies are required, though the ethics of randomised trials in this high-risk population have been questioned (Greenburg et al. 2009).

2.7.2.4 Oral appliances

Mandibular advancement devices (MAD) are considered the best alternative for individuals who are unwilling or unable to tolerate CPAP (Fleetham & Almeida 2010), and are the usual first-line treatment for primary snoring. An orthodontic gumshield-type device is worn over the teeth at night, pulling the lower jaw and attached soft tissues (including the tongue) forward, increasing the pharyngeal space. This is particularly useful in cases where snoring is caused by retrognathia. Side-effects including orofacial pain, excessive salivation and inability to retain the device have been described (Izci et al. 2005), and MAD use has been shown to be less effective than CPAP in individuals with mild/moderate OSAHS (Lam et al. 2007). However, in a recent randomised crossover trial of MAD in symptomatic individuals with mild/moderate OSAHS who had declined or did not require CPAP therapy, treatment with MAD was found to be effective, both in terms of clinical outcomes and health economics, in comparison to no treatment (Quinnell et al. 2014).

Other oral appliances which increase the pharyngeal space, including tongue retention devices which pull the tongue forward during sleep (Lazard et al. 2009) and oral pressure therapy which is applied over the lower teeth to protrude the jaw (Colrain et al. 2013) are available, though evidence for their efficacy is currently scant.

2.7.2.5 Positional therapy

The gravitational effect of lying in the supine position can impact on airway patency during sleep. Some individuals experience positional OSAHS in which apnoea/hypopnoea only occurs when lying on their back. In this instance, positional therapy may be appropriate. A positional training device, which vibrates whenever the patient turns onto their back and stops when they return to a non-supine position, has been shown to reduce AHI in individuals with mild/moderate positional OSAHS (Van Maanen et al. 2012).

2.7.2.6 Hypoglossal nerve stimulation

Stimulation of the hypoglossal nerve during inspiration using an implantable device triggers contraction of the genioglossus muscle, and the resulting tongue protrusion

counteracts airway narrowing. This has been shown to be both safe and effective in individuals with moderate/severe OSAHS for whom CPAP has been intolerable (Eastwood et al. 2011), though further studies are required.

2.8 Conclusion

OSAHS is a common condition which is related to increased morbidity and mortality. However, simple, effective treatment in the form of CPAP is available and, in most cases, significantly reduces or normalises the risks associated with the disorder. Whilst alternative treatments are available and desirable to patients, these are less effective than CPAP in most cases and are, therefore, only recommended for specific patient subpopulations, as an adjunct to CPAP therapy or in individuals who are non-compliant with CPAP.

Chapter 3: The relationship between DS and OSAHS

As the preceding chapters have shown, there is significant overlap between the DS phenotype and factors which contribute to OSAHS. This chapter outlines the relationship between the two disorders, and provides the context for the studies described within the remainder of thesis.

3.1 Prevalence of OSAHS in DS

The prevalence of OSAHS in adults with DS was undetermined at the outset of this work. However, there were a number of smaller studies in children with DS.

The first large study of over 100 children with DS aged 1-18 years used inpatient polygraphy to screen for OSA, independent of clinical suspicion of OSAHS (de Miguel-Díez et al. 2003). Fifty-five percent of children had OSA, defined as ≥3 apnoea/hypopnoea (AH) events per hour in bed. A gender effect was noted, with 65% of males and 39% of females exhibiting OSA. AH per hour in bed showed a significant association with younger age, male gender and tonsillar (but not adenoidal) hypertrophy; there was no correlation with obesity, congenital heart disease or previous adenotonsillectomy. An AHI of ≥1 event per hour of sleep is considered abnormal in children when using PSG. However, since AH can be diluted when using polygraphy (see Chapter 2), a higher AH cut-off may be required; in this study, use of an AH cut-off of ≥5 events per hour gave a prevalence of 42%, 23% at AH≥10 and 12% at AH≥15. Despite methodological and population differences across studies, the objective prevalence of OSAHS in the typically-developing paediatric population is estimated at 0.1-13.0% (Lumeng & Chervin 2012), much lower than was reported in the study of children with DS by de Miguel-Diez, regardless of AH cut-off.

To date, only two studies have used PSG to assess the prevalence of OSAHS in adults with DS. In a study in Italy (Resta et al 2003), six adults (3 male, 3 female) aged 28-53 with DS years from a residential facility underwent inpatient PSG after

an acclimatisation night. Using a diagnostic threshold of AHI≥10 events per hour, 5 of the 6 participants (83%) had OSA. Severity of OSA, measured by AHI or ODI, was not associated with age, BMI or neck circumference. A prevalence of 83% represents a substantial increase over the 2-4% observed in the general adult population (Young et al. 1993). However, this study has a number of significant limitations. Firstly, the very small number of participants should be noted. All participants lived in residential care and so the results may not be generalisable to the wider DS population, particularly given that residential status can affect health outcomes, including physical activity and BMI (Prasher 1995; Finlayson et al. 2009). Only two of the six individuals included in this study were overweight or obese using WHO criteria (World Health Organization 2006), the remaining four participants all being of normal BMI; again, this suggests that this data may not be generalisable to the wider DS population, where overweight and obesity affects up to three-quarters of individuals and differs according to gender (Prasher 1995; Van Allen et al. 1999; Melville et al. 2005; Melville et al. 2007; Henderson et al. 2007). Data relating to symptoms of OSAHS and ethnicity were not collected. None of the participants were taking any medication or had significant comorbidities, which, again, may not be representative of the DS population as a whole.

The second published study included 16 adults with DS aged 19-56 years recruited from a DS-specific clinic and DS advocacy groups in the USA (Trois et al. 2009). Except for one Asian participant, all were Caucasian. There was an even gender split, and 4 of the 8 females were post-menopausal. Three-quarters of participants were obese and 13% were overweight. The mean ESS was 12 (range = 3-20)/24, and 63% reported EDS. Using an AHI cut-off of >15 events per hour, all but 2 of the participants (88%) had OSAHS, with no significant gender difference. AHI was highly correlated with obesity, but not with age. Only one of the 16 participants had been referred for evaluation of possible OSAHS, despite the majority of participants being found to have severe OSAHS. Although this more rigorous study is slightly more representative of the DS population than the study by Resta et al (Resta et al. 2003), the major limitation is, again, the very small number of participants.

One further study recruited 12 young adults with DS from a DS day centre in Greece and conducted PSG in the participants' own homes (Andreou et al. 2002). Using an AHI threshold of >10 events per hour, 100% of participants had OSA, though the ESS was normal in all cases.

These studies suggest that the prevalence of OSAHS in the DS population is greatly elevated, but small participant numbers and methodological issues underline the need for larger, population-based studies. This is the basis for the studies discussed in Chapter 5-7 of this thesis.

3.2 Comorbidities

3.2.1 Anatomy and physiology

The characteristic craniofacial phenotype of individuals with DS, 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. This has been demonstrated using MRI in children with DS (Uong et al. 2001; Shott & Donnelly 2004; Donnelly et al. 2004; Guimaraes et al. 2008). Being overweight or obese is the most important risk factor for OSAHS, and up to three-quarters of adults with DS fall into this category.

It is likely that premature ageing evident in individuals with DS exacerbates the age-related increase in OSAHS risk seen in the general population, and the increasing life expectancy of individuals with DS means that the number of adults with DS living with OSAHS is likely to increase over the coming years.

3.2.2 Cognitive impairment

As discussed in Chapter 2, untreated OSAHS leads to cognitive impairment. Given that adults with DS are already cognitively impaired by virtue of their ID, the impact of OSAHS in this population may be even more pronounced. A study in children aged 7-12 years with DS using the Arizona Cognitive Test Battery found that those

with comorbid OSAHS performed less well on a test of executive function and had a mean verbal IQ score 9 points lower than those without; no association with age or BMI was noted (Breslin et al. 2014). In a small sample of adults with DS, AHI was associated with poorer performance in right hemisphere-related visuoperceptual skills tasks (Andreou et al. 2002).

Individuals with 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 (Alchanatis et al. 2005); therefore, it is likely that those with DS who have IQ below the normal range will be more susceptible to the cognitive impact of OSAHS due to their reduced reserve. There is evidence that higher cognitive reserve can reduce the risk of Alzheimer's disease in the ageing general population (Stern 2012), while, in adults with DS, early-onset Alzheimer's-type dementia is almost universal by the age of 40 years (Lai & Williams 1989). There appears to be overlap between the brain regions which are structurally and functionally affected in DS with those which are impaired in OSAHS in the general population, particularly the hippocampus and prefrontal cortex. Overall, the combination of ID, early-onset dementia and OSAHS may leave adults with DS extremely vulnerable to cognitive impairment. Fernandez and Edgin proposed the hypothesis that untreated OSAHS accelerates the cognitive decline associated with ageing in adults with DS (Fernandez & Edgin 2013). They suggest that sleep fragmentation disrupts sleep-dependent memory consolidation during slow wave sleep, whilst intermittent hypoxia causes neuronal damage and promotes amyloid deposition. It is possible that CPAP therapy may decelerate age-related cognitive decline in adults with DS and OSAHS by alleviating sleep fragmentation and intermittent hypoxia. While there are no formal studies in this population, CPAP has been shown to reduce sleep fragmentation and increase the percentage of slow wave sleep in non-DS adults with mild/moderate Alzheimer's disease and OSAHS (Cooke et al. 2009).

Untreated OSAHS is related to behavioural and emotional disturbances in children and adults with DS (Capone et al. 2006; Dykens 2007), and depression is common in both individuals with DS and in typically-developing adults with OSAHS. A survey of twenty eight adolescents and young adults with DS diagnosed with major

depression by a mental health clinic for people with DS found that 86% had OSAHS when tested by PSG, in comparison with 44% of non-depressed controls; moderate/severe OSAHS was evident in 54% of cases and 11% of controls (Capone et al. 2013). Though this study had not been published at the time that our work commenced, this suggests that the coexistence of both DS and OSAHS may increase the risk of mood disturbance and depression, given that rates of depression have been quoted as 6-46% in DS irrespective of OSAHS (Holland et al. 1998; Roizen & Patterson 2003; McCarron et al. 2005; Mantry et al. 2007; Virji-Babul et al. 2007; Kerins et al. 2008) and 32-57% in those with OSAHS in the non-DS population (Harris et al. 2009; Reyes-Zuniga 2012; Douglas et al. 2013).

DS and OSAHS are both independently associated with cognitive impairment, and it appears that the presence of both may amplify the level of impairment observed.

3.2.3 Pulmonary Hypertension

Pulmonary hypertension can result from or be worsened by untreated OSAHS in individuals with DS, and should be considered as a possible underlying cause when unexplained pulmonary hypertension is noted (Levine & Simpser 1982; Marcus et al. 1991; Lefaivre et al. 1997).

3.2.4 Genetic predisposition

OSAHS is known to have a hereditary component, as discussed in Chapter 2, with genetic factors explaining around 40% of the variance in AHI in the general population (Redline & Tishler 2000). Since individuals with DS display phenotypic features of both familial genes and the DS genotype, it could be posited that a family history of OSAHS might compound the risk of OSAHS in these individuals.

3.2.5 Immune dysfunction

Individuals with DS have impaired immune function from birth which can lead to recurrent infections (Charleton et al. 2010). OSAHS can contribute to recurrent infections in individuals with DS due to sleep disruption (Ram & Chinen 2011). Sleep disruption has been associated with immune dysfunction in the general population (Bryant et al. 2004).

3.3 Treatment of OSAHS in DS

To date, there are no randomised, controlled trials assessing the effects of CPAP treatment in children or adults with DS and OSAHS.

In children, the first-line treatment for OSAHS is adenotonsillectomy (Schechter 2002). A small study of 11 children with DS and OSAHS, mean age 8.5 years, found that adenotonsillectomy resulted in a significant decrease in AHI, though to a lesser degree than in a control group children without DS (Shete et al. 2010). The SpO_2 nadir was improved in children without DS, but not in the DS group. Neither group showed an improvement in arousal index post-tonsillectomy. No further treatment was required in the non-DS group, but 55% of the DS group required CPAP therapy for residual OSAHS.

A study of the effect of 3 months of CPAP therapy in children with OSAHS included a subset of 10 children with neurodevelopmental disorders – 6 with DS and one child each with Prader-Willi syndrome, cerebral palsy, autism and a complex chromosomal disorder (Marcus et al. 2012). In the developmentally delayed group, CPAP use was associated with significant improvements in subjective sleepiness, behaviour and quality of life. However, the anthropometric data, sleep characteristics or CPAP compliance of this subgroup were reported separately, and the small sample number and heterogeneity of neurodevelopmental disorders mean that this cannot necessarily be generalised to the wider paediatric DS population.

Trois et al reported anecdotally on the outcome of CPAP therapy in 14 adults with DS identified as having OSAHS (Trois et al. 2009). Of the 14 individuals, 9 were followed up clinically by the study team, 1 sought treatment elsewhere and the outcome of the remaining 4 was unknown. Eight of the 9 individuals underwent CPAP titration (one did not attend); of these, 7 commenced fixed-pressure CPAP at a pressure of 7-10cmH_2O and one individual with severe OSAHS commenced bilevel ventilation. Five of the 8 adults on treatment had an excellent compliance of 6-8 hours per night, with their families reporting a subjective improvement in sleepiness and daytime function. One participant had a compliance of only 2 hours per night,

one refused treatment due to anxiety and one quit CPAP due to nasal congestion. No formal subjective or objective measures of CPAP efficacy were made.

Given that over half of children with DS and OSAHS require CPAP despite adenotonsillectomy and that the likely prevalence of OSAHS in adults with DS is so high, it is perhaps surprising that so little evidence relating to efficacy or acceptability of CPAP exists.

3.4 Screening for OSAHS

Guidelines published by the Royal College of Paediatrics and Child Health recommend that all children with DS should be offered a screening test using at least overnight oximetry at least once in infancy and annually until the age of 3-5years (Royal College of Paediatrics and Child Health 2009). In the event of an abnormal oximetry study, polygraphy or polysomnography should be performed. Screening until 3-5 years was chosen arbitrarily in the absence of any evidence that further screening of asymptomatic children was warranted, and in the belief that covers the period of highest risk for OSAHS. However, it is important that families are made aware of the symptoms of OSAHS and that these are not overlooked by parents or professionals, or subject to diagnostic overshadowing (Reiss et al. 1982). Symptoms of OSAHS should continue to be monitored across the lifespan (Van Allen et al. 1999; Smith 2001; Roizen & Patterson 2003; Charleton et al. 2010; Bull 2011). The Down's Syndrome Association published a DS Health Book for adults with DS to carry with them to annual health checks with their GP (Down's Syndrome Association 2014). This allows the individual to take ownership of their own health and wellbeing and acts as a guide for GPs regarding required health checks; this includes reference to sleep problems including OSAHS, and additional guidance for GPs is provided via a website (Hill 2013). However, given the healthcare inequalities facing adults with DS and the fact that guidelines for health surveillance in adults with DS are not always adequately followed (see Section 1.4.4 for discussion), education of individuals with DS, their families and healthcare professionals by providing an adequate evidence to support this endeavour is vital.

3.5 Conclusion

Despite a clearly increased risk of OSAHS in adults with DS and some overlap between the deleterious consequences of both disorders, neither prevalence of OSAHS in adults with DS nor the effect of treatment with CPAP in this population has been systematically documented in a large cohort. The remaining chapters of this thesis document our attempts to address these gaps in the evidence.

Chapter 4: Aims, research questions and ethics

This chapter summarises the aims and objectives of the study, and the ethical approval required.

4.1 Study design

The study was designed in two parts. The first part of the study was an assessment of the prevalence of SDB across the target population using subjective and objective measures. The second part of the study was a single-blind, randomised parallel/crossover trial of CPAP therapy versus conservative lifestyle measures for treatment of OSAHS, allowing both between-groups and within-groups comparisons. The methodology used to deliver the both parts of the study is described in detail in Chapters 5-8.

4.2 Aims

The aims of this study was two-fold:

1. To systematically document the prevalence of OSAHS in a population of adults with DS.
2. To assess the efficacy of CPAP therapy in adult patients with OSAHS and DS, including formal assessment of symptomatic relief, treatment response and functional status.

4.3 Research questions

To meet these aims, three research questions were considered:

1. What is the prevalence of OSAHS in adults with DS in Scotland (and the UK)?
2. Does CPAP use in DS adults with OSAHS improve sleepiness and quality of life more effectively than lifestyle measures alone?

3. What are the potential barriers to implementing CPAP effectively in DS adults with OSAHS?

4.4 Primary and secondary outcomes

4.4.1 Primary outcomes

The primary endpoint of the treatment phase of the study was the change in subjective sleepiness, as measured by the Epworth Sleepiness Scale (ESS) (Johns 1991), from baseline to 1month. The ESS is a robust index, widely used in both clinical practice and clinical trials. A change of 1 point on the ESS is the smallest detectable shift in the score (which is a categorical scale with one point increments) and is the minimum clinically significant change since it is indicative of one symptom state shift on one domain of the score. A pictorial version of the ESS, designed for use with patients with diminished literacy skills, has been shown to produce scores comparable with the traditional ESS (Ghiassi et al. 2010), and was implemented during this study. Both questionnaires will be discussed in more detail in Chapter 5.

4.4.2 Secondary outcomes

A number of secondary outcomes were assessed. All instruments are discussed in further detail in Chapters 5 and 8.

1. Change in subjective sleepiness (pESS) from baseline to 3, 6 and 12 month visits.
2. Objective changes in emotional and behavioural function, measured using a modified version of the Developmental Behaviour Checklist for Adults (Mohr et al. 2005).
3. Health status and quality of life, measured by the RAND-36 instrument (Hays et al. 1993).
4. Cognitive function, measured using the Arizona Cognitive Test Battery (Edgin et al. 2010).
5. Adverse events, including side effects associated with CPAP usage.

6. Compliance with CPAP, reported as the average hours of use per night, along with other data recorded by in-built machine software. Periods for which the machine is on and being used are recorded, and provide the gold standard method for monitoring CPAP compliance.
7. Carer burden, measured using a modified version of the Zarit Burden Inventory (Bédard et al. 2001), 12-item version of the General Health Questionnaire (Goldberg 1972) and open-ended qualitative questions about the experience of caring.

4.4.3 Sample size

An estimate of required sample size was made with the input of the trial statistician. Given that the likely effect size was unknown, a conservative estimate of effect size related to variability was made. A sample size of 70 participants was proposed, based on a previous repeated measures, parallel-arm, intention-to-treat study within the department, investigating the effects of CPAP on daytime function in adults with OSAHS in the general population (McFadyen et al. 2001). It was calculated that this sample size would provide 90% power to detect large differences of 0.8 SD between treatment groups and 90% power to show moderate r-values of >0.5 within the CPAP-only group. Given the finite population of adults with DS, we aimed to recruit a minimum of 26 participants into each arm of the study to achieve a power of 80%, with 34 participants in each arm giving a power of 90%. It was thought that this number should be achievable, given expertise of the study team in recruiting for previous studies and estimating that over 50% of the adult DS population would have OSAHS. With no available data on CPAP compliance in individuals with DS, a non-compliance rate of 10% was estimated, based on previous studies within the department, with any participant withdrawals resulting in a small decrement in study power.

4.5 Ethical approval and informed consent

Ethical approval was sought from the Scotland A Research Ethics Committee (REC), the national NHS REC specialising in review of studies involving adults with incapacity to give consent (AWI).

The initial ethics application sought approval to include a full cross-section of the target population, including adults with capacity to consent and AWI. However, the ethics committee felt that there was insufficient evidence that the inclusion of AWI could be permitted within the scope of the Adults With Incapacity (Scotland) Act 2000 (Scottish Parliament 2000), and approval for the study was given only with the exclusion of AWI from the treatment phase of the study. The questionnaire study was approved for people with and without capacity to consent, and no formal informed consent was required for this phase of the study; return of a completed questionnaire was considered implicit consent.

Substantial amendment notices with additional evidence supporting the inclusion of AWI in the treatment study were submitted, but not successfully approved until March 2013, at the third attempt (15 months from first recruitment). This proved to be a significant obstacle to study progress, and is discussed in further detail in Chapter 9.

Prior to March 2013, informed consent to participate in the treatment study was obtained prior to the initiation of any study-specific procedures (i.e. prior to issue of the home sleep study equipment) using a written consent form signed by the participant (see Appendix 2). On the first visit, the study procedures were reviewed with the participant and their relative/carer, using simple language and augmented with signs and gestures to enhance understanding. Prior to the first visit, the families received a copy of the patient and carer information sheets by post; care was taken to ensure that the families had read these documents, and spare copies were offered if required. The consent form, written in easy-read format, was explained to the participant and relative/carer. All parties were invited to ask any questions and raise any concerns prior to signing the consent form. Assessment of the participant's ability to give informed consent was made on a case-by-case basis by the researcher, and anyone deemed unable to consent was excluded from the study. Individuals who were subject to a guardianship order or whose relative/carer held welfare power of attorney for the individual were automatically excluded from participation since both of these legal positions are only granted when a person lacks capacity to consent.

After the ethics decision to allow inclusion of AWI, additional consenting procedures were required, which varied depending on where the participants study procedures were conducted and whether they were able to give consent for themselves. All participants assessed as having capacity to consent signed a consent form as above.

For all Scotland-based patients lacking capacity, and patients lacking capacity from outwith Scotland travelling to Edinburgh to participate in the research, consent was obtained on their behalf in keeping with the Adults with Incapacity (Scotland) Act (Scottish Parliament 2000) using a separate consent form for AWI (see Appendix 2). Consent was taken from their nearest relative if they had one, and if they did not, from their welfare attorney. Although the term welfare attorney is not used in England, Wales or Northern Ireland, the principle is the same in that there will be a person nominated who takes care of the person's affairs, and who, when they are in Scotland, can be considered, in principle, a welfare attorney.

For patients lacking capacity from outwith Scotland who will be visited in their home or another non-NHS location, appropriate ethical approval was sought from a relevant ethics committee in England and/or Northern Ireland as required. Advice was sought from the participant's consultee in line with the Mental Capacity Act 2005 in England and Wales (HM Government 2005), or assent sought from a close relative or friend of the person lacking capacity to consent in line with Northern Ireland common law (NHS Health Research Authority 2015).

In line with the recommendations of the Duke Down's Syndrome Research Team (Heller et al. 2006), informed consent was obtained at a visit where no other test procedures were to be carried out (other than issue of home sleep study kit), allowing the investigators to establish a rapport with the participant and their relative/carer, familiarising them with the study environment and reducing anxiety.

The original signed copy of the consent form was filed and stored securely within the Sleep Research Unit, with a photocopy of the signed form sent to the participant and their carer for their records. Further copies were filed in the participant's case report form and NHS Lothian patient casenotes as appropriate.

Chapter 5: Subjective assessment of prevalence – Questionnaire study

The first part of the study was a cross-sectional population study designed to assess prevalence of SDB/OSAHS in adults with DS using subjective measures.

5.1 Methods

The study prevalence questionnaire is included in Appendix 1. Since, as discussed in Chapter 1, there is a wide spectrum of ID in DS and, commonly, visual impairments, it was important to ensure the questionnaire was as accessible to as many people with DS as possible; although the questionnaire states that the participant may seek help from a relative or carer if required, we were keen to obtain a response from the participant themselves wherever possible. The questionnaire, therefore, was written in easy-read format. There is evidence that the use of easy-read information can enhance understanding and retention of medical and health information, and improve compliance (Houts et al. 2006).

Guidance on easy-read formats was sought from FAIR Advice (www.fairadvice.org.uk), an Edinburgh-based charitable organisation providing an information and advice service for people with ID, parents, carers and professionals. The organisation also publishes easy-read health information booklets specifically designed for people with ID, including a number of booklets commissioned by NHS Scotland. Two FAIR booklets were subsequently included in the lifestyle advice package for the randomised treatment study, and are discussed in further detail in Chapter 8. Guidance published by the Department of Health was also considered (Department of Health 2010).

A minimum 14-point font was used to enhance visibility for those with visual impairments. Simple language was used as far as possible, although some elements of the questionnaire could not be simplified without losing functionality. Where possible, pictorial information was used to enhance accessibility and understanding.

All study documents were reviewed for ease of understanding by a group of people with DS assembled via and facilitated by Down's Syndrome Scotland (DS Scotland; www.dsscotland.org.uk), a national charity supporting individuals with DS and their families. Changes suggested by the group and DS Scotland staff were used to refine the questionnaire and other study documentation prior to distribution.

The questionnaire was designed in two parts, with one section for completion by the participant with DS and a second section for completion by a relative or carer who knew the participant well.

5.1.1 Demographics and general health

The participant section of the questionnaire asked about demographic information including age, height, weight, collar size and smoking status. Presence of comorbidities associated with DS and sleep disturbances, including thyroid status, previous ENT surgery, diabetes and cardiovascular, respiratory and gastro-intestinal problems was assessed via tick-box, and participants were asked to list any current prescribed and non-prescribed medications. Medications were categorised using the World Health Organisation Anatomical Therapeutic Chemical Classification System (ATC-DDD) (WHO Collaborating Centre for Drug Statistics Methodology 2011). Participants were asked to note any diagnosed sleep disorders, along with current or previous treatment of these.

5.1.2 Modified sleep questionnaire

Sleep disturbances were recorded using a modified version of an in-house sleep questionnaire. Although not formally validated, this questionnaire has been used routinely in our Department for over 30 years as a pre-assessment tool in patients referred clinically for assessment of possible sleep disorders including SDB, OSAHS, narcolepsy and parasomnias, as well as in a number of research studies (Engleman et al. 1994; Kingshott et al. 1995; Kingshott et al. 1998; Engleman et al. 1998; McArdle et al. 1999). Elements of the questionnaire relating to sleep duration and phenomena of disturbed sleep were selected and presented in easy-read format. Participants were asked to document the number of hours per twenty-four hours that they spent asleep during the night and during the day. Presence of snoring, witnessed

apnoeas, nocturnal choking episodes, frequent awakenings, unrefreshing sleep and daytime sleepiness were rated on a Likert-type scale based on the number of nights per week each phenomenon occurred.

5.1.3 Pictorial Epworth Sleepiness Scale

The Epworth Sleepiness Scale (ESS) (Johns 1991) is a standard instrument used to assess daytime sleepiness in the general population. This validated tool has been routinely employed in clinical and research practice since its development in the 1990s. Advantages of the ESS include its brevity and simplicity. The single-page questionnaire (Figure 16) can be quickly and easily completed by most patients, and easily scored and interpreted by the clinician. The ease of use of the ESS and its reliability as a repeated measure to track changes in subjective sleepiness over time and pre/post-intervention has resulted in its widespread use.

The individual is asked to rate their likelihood of dozing or falling asleep (in contrast to just feeling tired) on a scale of 0-3, where 0 = would never doze and 3 = would definitely doze, in a set of eight everyday scenarios: sitting reading; watching TV; sitting inactive in a public place; as a passenger in a car for an hour without a break; lying down to rest in the afternoon; sitting talking to someone; sitting quietly after a lunch without alcohol; and in a car whilst stopped for a few minutes in traffic. The reference period relates to “recent times”. Individual scores for each of the eight items are added together to give a total score in the range 0-24. The generally-accepted cut-off for an abnormal score on the ESS is >10/24 (Johns 1993; Rosenthal & Dolan 2008).

Sensitivity and specificity of the ESS have been shown to be high (sensitivity 93.5%, specificity 100%) in individuals with narcolepsy (Johns 2000), a population which has been shown to be 5 times sleepier than controls (Parkes et al. 1998). Sensitivity and specificity are lower in patients with OSA (66% and 48% respectively) with an area under the ROC curve of 0.6 when OSA is defined as an AHI>5 (Rosenthal & Dolan 2008). ESS scores show good test-retest reliability, with no significant difference and high correlation between scores in control participants over time, and a reduction in individuals with OSAHS treated with CPAP (Johns 1992). A meta-

analysis (n=706) of the effect of CPAP therapy on sleepiness associated with OSA showed a significant reduction in ESS overall, with CPAP use reducing the ESS by a mean of 3 points more than placebo overall and by 5 points in individuals with severe OSA (Patel et al. 2003).

Although the ESS is generally well understood and completed, understanding is reliant upon the ability to read and write; persons with diminished literacy skills, including people with ID may have problems understanding and completing the questionnaire. To address these issues, a pictorial version of the ESS (pESS) was devised (Ghiassi et al. 2010), aiming to enhance understanding and accessibility of the ESS in people with and without diminished literacy in the general population. Both the original ESS and the pESS are shown in Figure 16.

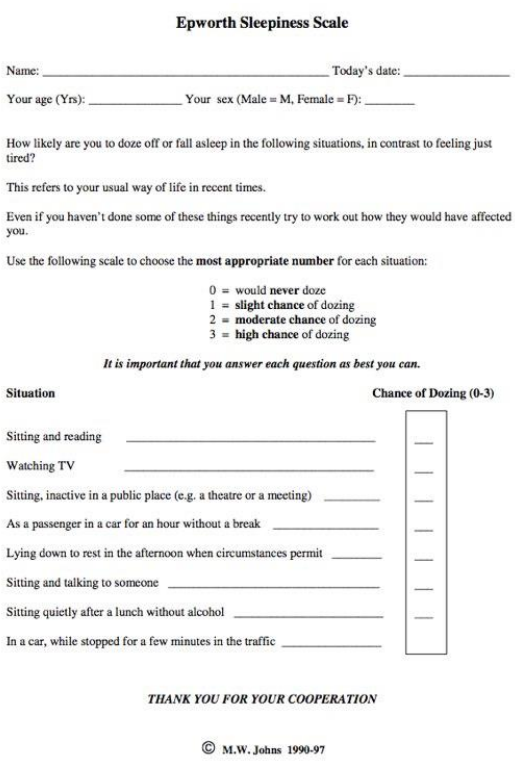
In the original validation study, scores on the pESS show good agreement with those on the original ESS, with 55% of participants who completed both scales expressing a preference for the pictorial version. The study did not specifically assess the utility of the pESS in persons with ID. However, given the known benefits of easy-read literature (Houts et al. 2006) and pictorial information in this patient group (van Schrojenstein Lantman-de Valk & Walsh 2008), we opted to use the pESS in our prevalence study.

Although designed to be self-completed, the ESS is frequently used as a proxy measure in clinical practice, for example by asking both the patient and their spouse, bed partner or relative to rate the patient's sleepiness. A number of studies (Johns 1994; Kingshott et al. 1995; Walter et al. 2002; Kumru et al. 2004) have examined use of the ESS as a proxy measure. Results suggest that, whilst neither patient nor proxy ESS scores are accurate predictors of objective sleepiness, obtaining both a patient and proxy ESS rating may give a more accurate picture of the patient's sleepiness. These studies have shown that scores on the ESS as rated by the patient or their proxy either do not significantly differ (Johns 1994; Kingshott et al. 1995) or tend to be higher when rated by a partner (Walter et al. 2002; Kumru et al. 2004), suggesting an element of underscoring of the severity of sleepiness by patients themselves. Therefore, it was anticipated that pESS scores provided via the

prevalence questionnaire would be either an accurate reflection of the person with DS's sleepiness or a conservative estimate, regardless of whether the questionnaire was completed by the individual or their relative/carer.

Although the ESS has not been specifically validated in the DS population, it has been used as a proxy measure in a previous study in adults with DS (Trois et al. 2009).

Figure 16: The original Epworth Sleepiness Scale (Johns 1991)and Pictorial Epworth Sleepiness Scale (Ghiassi et al. 2010). Original ESS used with written permission from MW Johns. Pictorial ESS reproduced from Thorax, Ghiassi R et al, 66: 97-100, 2011 with permission from BMJ Publishing Group Ltd.



Epworth Sleepiness Scale

Name: _____ Today's date: _____

Your age (Yrs): _____ Your sex (Male = M, Female = F): _____

How likely are you to doze off or fall asleep in the following situations, in contrast to feeling just tired?

This refers to your usual way of life in recent times.

Even if you haven't done some of these things recently try to work out how they would have affected you.

Use the following scale to choose the **most appropriate number** for each situation:

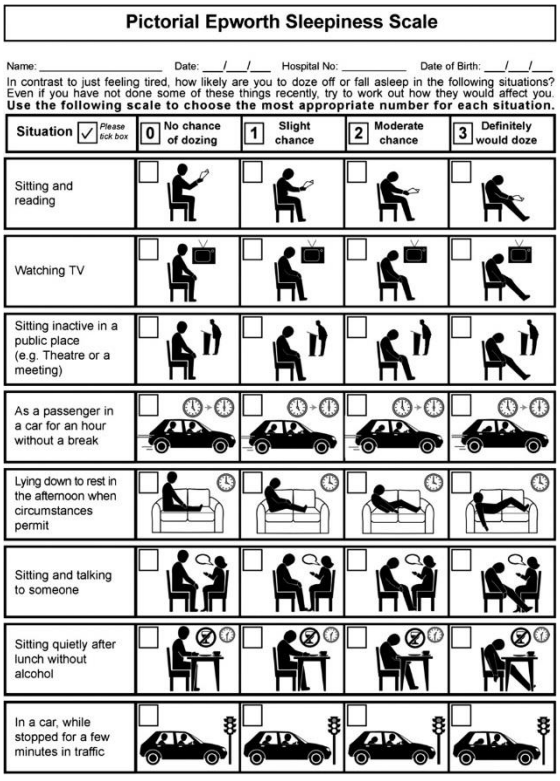
0 = would **never** doze
1 = **slight chance** of dozing
2 = **moderate chance** of dozing
3 = **high chance** of dozing

It is important that you answer each question as best you can.

Situation	Chance of Dozing (0-3)
Sitting and reading	
Watching TV	
Sitting, inactive in a public place (e.g. a theatre or a meeting)	
As a passenger in a car for an hour without a break	
Lying down to rest in the afternoon when circumstances permit	
Sitting and talking to someone	
Sitting quietly after a lunch without alcohol	
In a car, while stopped for a few minutes in the traffic	

THANK YOU FOR YOUR COOPERATION

© M.W. Johns 1990-97



Pictorial Epworth Sleepiness Scale

Name: _____ Date: ___/___/___ Hospital No: _____ Date of Birth: ___/___/___

In contrast to just feeling tired, how likely are you to doze off or fall asleep in the following situations? Even if you have not done some of these things recently, try to work out how they would affect you.
Use the following scale to choose the most appropriate number for each situation.

Situation (Please tick box)	0 No chance of dozing	1 Slight chance	2 Moderate chance	3 Definitely would doze
Sitting and reading	☐	☐	☐	☐
Watching TV	☐	☐	☐	☐
Sitting inactive in a public place (e.g. Theatre or a meeting)	☐	☐	☐	☐
As a passenger in a car for an hour without a break	☐	☐	☐	☐
Lying down to rest in the afternoon when circumstances permit	☐	☐	☐	☐
Sitting and talking to someone	☐	☐	☐	☐
Sitting quietly after lunch without alcohol	☐	☐	☐	☐
In a car, while stopped for a few minutes in traffic	☐	☐	☐	☐

5.1.4 Modified Developmental Behaviour Checklist for Adults

The final section of the questionnaire, directed at the carer or relative of the person with DS, was an abbreviated version of the Developmental Behaviour Checklist for Adults (DBC-A). The Developmental Behaviour Checklist (DBC) (Einfeld & Tonge 1995) is a suite of instruments for assessment of behavioural and emotional disturbances in children, adolescents and adults with developmental disabilities and ID. It has been used to track changes in behavioural/emotional disturbances over time in young people with ID, including people with DS (Tonge & Einfeld 2000; Clarke et al. 2003).

Originally comprising the Primary Carer Version (DBC-P) and Teacher Version (DBC-T) (Einfeld & Tonge 2002), a revised version for adults with ID, the DBC-A, was published in 2004 (Mohr et al. 2005). The DBC-A was adapted from the DBC-P, and comprises 107 items examining a range of behavioural and emotional disturbances, designed to be answered by a relative or carer who knows the person with ID well. Each item is scored on a scale of 0-2, where 0 = “not true as far as you know”, 1 = “somewhat or sometimes true” and 2 = “very true or often true”, based on the person’s behavioural and emotional state over the preceding 6 months. Items are grouped into 6 subscales representing different dimensions of disturbance: Disruptive; Self-absorbed; Communication Disturbance; Anxiety/Antisocial; Social Relating; Depressive.

The DBC-A can be scored at 3 broad levels: the overall score, individual subscale scores or individual item scores. To keep the prevalence questionnaire as concise as possible, we opted to include three of the six subscales, which, based on a previous study (Riha et al. 2006) were most closely related to sleep disturbance: Disruptive, Anxiety/Antisocial and Depressive. Behaviours in the Disruptive category include irritability, impatience and impulsivity. Antisocial behaviours include stealing, stubbornness and being bossy. Depressive behaviours include poor self-esteem, becoming withdrawn and loss of appetite. The full list of questions included is shown in the questionnaire in Appendix 1.

The DBC-A has been shown to be both reliable and valid, with specificity = 0.69, specificity = 0.79 and area under the ROC curve of 0.77. Scores on the DBC-A have been shown to correlate highly with other validated measures of behavioural and emotional disturbances in adults with ID, including the Aberrant Behaviour Checklist (ABC) and Psychiatric Assessment Schedule for Adults with Developmental Disability (PAS-ADD).Validation studies have shown the DBC-A has acceptable test-retest and inter-rater reliability, as well as high internal consistency, in both family members and paid carers (Mohr et al. 2005).

The DBC-A subscale totals are calculated by adding the scores for all questions in each domain, except the Anxiety/Antisocial subscale, in which all scores were totalled with the exception of "Poor sense of danger", which was subtracted.

Data from each DBC-A subscale can be compared in a number of ways. Although reporting the total score (sum of item scores; SIS) on each subscale is a very simple method of comparing an overall summary of problem behaviours within and between individuals, it does not give information on the number of individual items checked or the scale at which these items are scored or the severity at which each behaviour is rated. For example, a total score of 10 could result from 10 individual behaviours scored at 1, 5 behaviours scored at 2 or a combination of 0, 1 and 2 scores, and it can be argued that an individual exhibiting a wider range of mildly problematic behaviours has a different profile from that of an individual with fewer but more severe behavioural problems. To extract more meaningful information on the extent and intensity level of problem behaviours from the DBC than total scores alone, Taffe et al (Taffe et al. 2008) describe the use of mean item scores (MIS), proportion of items checked (PIC) and intensity index (II).

The mean item score (MIS) is calculated by dividing the SIS by the number of items in the subscale, and represents the average level of overall problem behaviour. The proportion of items checked (PIC) is the number of positive responses (scores of 1 or 2) divided by total number of items in scale, which indicates the breadth of range of behaviours exhibited. The MIS and PIC Scores can be combined to give an intensity index (II; MIS/PIC-1); MIS = PIC(1 + II); this represents the proportion of

positively-scored items scored as somewhat or often true, and gives a measure of the intensity of problem behaviour.

Normative data on the DBC-A for adults with ID aged 18-85 years, stratified by level of ID, were collected in 2009 and released in 2011(Mohr et al. 2012), allowing comparison of total problem behaviour scores, mean item scores and individual subscale scores to the population norms. At this time, the subscales and factors of the questionnaire were updated and renamed on the basis of the new data. Since this change was made after commencement of our study, we used the original DBC-A (Mohr et al. 2005) rather than the new version. Unfortunately, the published normative data are not applicable to the original version of the DBC-A, and so normative data are unavailable the version of the checklist used in this study.

5.1.5 Symptoms suggestive of OSA

Symptoms highly suggestive of OSA were defined using 3 algorithms based on those validated in a recent questionnaire-based survey of prevalence of OSA in the French general population (Fuhrman et al. 2012). These algorithms use combinations of recognised symptoms to identify individuals who have a high probability of OSA:

1. Snoring ≥3 nights per week plus (witnessed apnoeas, or pESS>10).
2. Snoring ≥3 nights per week plus (witnessed apnoeas, or unrefreshing sleep ≥3 nights per week).
3. Snoring ≥3 nights per week plus (witnessed apnoeas, or daytime sleepiness ≥3 nights per week).

5.1.6 Identification of participants and distribution of questionnaires

Easy-read invitation leaflets and questionnaires (see Appendix 1) were sent initially to a community-based sample of adults (age ≥16 years, the age of legal adulthood in Scotland (Scottish Government 1991)) with DS in Scotland, commencing in February 2011. Participants and their relative/carers were invited to complete and return a questionnaire, indicating via a check box if they did not wish to be contacted

with regards to undergoing a home sleep study at a future date. A pre-paid return postage envelope was provided.

All questionnaires, return postage envelopes and mailing envelopes were individually numbered to allow identification of participants whilst maintaining anonymity. Numbers were allocated sequentially from DSQ0001-DSQ5430 (with DSQ an acronym for Down syndrome questionnaire). The numbered questionnaires were mailed out on behalf of the research team by a number of third-party organisations working with people with DS. The research team did not have access to the personal details of any potential participants identified by these outside organisations until such time as a completed questionnaire was returned, if the participant chose to disclose this. Each outside organisation was asked to keep an on-site list of participants contacted and their individual questionnaire numbers to ensure that each participant could be tracked and contacted again as required on behalf of the study team. Numbers on return envelopes allowed identification of individual participants for further contact even if they did not provide their name and/or address on the questionnaire.

Individuals with DS aged ≥16 years were primarily identified by DS Scotland from their membership database. Further individuals were identified and contacted by the NHS Greater Glasgow and Clyde Primary Care Liaison Team, who hold a database of adults with ID in the Greater Glasgow and Clyde area, and Sleep Scotland (www.sleepscotland.org), a charity providing support to families of children and young people with additional support needs and severe sleep problems, who hold a database of individuals who have accessed their service. A number of other organisations working with people with DS also identified smaller groups of participants. Current and previous clinical patients attending or known to the Department of Sleep Medicine, Royal Infirmary of Edinburgh, who met the study criteria were contacted directly by the research team. Patients known to be on CPAP treatment were sent prevalence questionnaires regardless of their ineligibility for the treatment phase of the study. Any eligible participants contacting the researchers as a result of publicity, advertising or word of mouth were sent a questionnaire directly by the study team.

A reminder letter and second questionnaire were sent out to anyone not returning a questionnaire within 2 months of the original mail-out, again by the distributing organisations to maintain anonymity. Prior to sending a postal reminder, DS Scotland sent an email reminder to anyone who had not returned a questionnaire for whom they had an email address. No further reminders were sent if no response was received after the second questionnaire.

In an extension to the original prevalence questionnaire study in Scotland, the same questionnaire was sent out to adults aged ≥16 years with DS across the rest of the UK (England, Wales and Northern Ireland), commencing May 2012. As per the Scotland survey, questionnaire distribution was completed anonymously on behalf of the research team by charitable organisations supporting people with DS and their families: the Down's Syndrome Association (DSA; www.downs-syndrome.org.uk) and the Down's Heart Group (www.dhg.org.uk). Again, a reminder letter and second questionnaire were sent out anonymously by the distributing organisations to anyone not returning a questionnaire in response to the original mailing, with no further reminders or contact made if no response was received after the second questionnaire. DSA declined to send a second questionnaire or email reminder.

The final prevalence questionnaires were posted out in June 2014.

As well as direct participant identification as described above, a number of publicity strategies were employed. Information on the study was included in publications by a number of organisations working with people with DS, allowing individuals interested in participating to contact the study team directly to have a questionnaire sent out and raising awareness of the study amongst professionals. This included the DS Scotland website, e-bulletins and magazine, FAIR Advice newsletter and Blackburn Support Services newsletter. A paid advertisement was placed in Third Force News (TFN), Scotland's only dedicated weekly newspaper for charities and voluntary organisations, with a readership of over 19000 people. A press release through the University of Edinburgh press office in April 2011 resulted in articles in local and national publications, including TFN, Metro, Edinburgh Evening News, Dalkeith Advertiser and Edinburgh University Science Magazine (EU:Sci). Posters

advertising the study were displayed on noticeboards throughout the Royal Infirmary of Edinburgh. Flyers promoting the study were distributed to professional groups and at meetings relating to sleep and/or DS, including: the Edinburgh Sleep Medicine Course; Scottish Sleep Forum; Scottish Senior Nurse Group; Down's Syndrome Medical Interest Group (DSMIG); Royal Society of Medicine meeting – "Dementia in people with intellectual disabilities: Getting it right"; and the London Dementia in Intellectual Disabilities Special Interest Group national conference.

As the study progressed, visibility of the study was enhanced via a number of professional presentations and public engagement activities. These are detailed in Appendix 4 and included: Royal Infirmary of Edinburgh Grand Rounds; DSMIG meeting, Winchester; European Society of Sleep Technologists meeting, Paris; and a workshop for people with DS, parents and carers at the DS Scotland conference, Cumbernauld. Longer articles related to the study were published in the British Sleep Society Newsletter and the DS Scotland magazine, Full Potential.

A number of abstracts were submitted and accepted for oral and poster presentations at national and international conferences; these are collated in Appendix 4.

5.1.7 Statistical analysis

All statistical analysis was overseen by an experienced Trial Statistician, Dr Linda J. Williams, Centre for Population Health Sciences, The University of Edinburgh (see Acknowledgements). Basic statistical analysis was conducted by the Investigator under the guidance of the Trial Statistician. More complex analyses were conducted by the Statistician for demonstration, with the Investigator replicating these tests and the Statistician checking for accuracy.

Standard statistical analyses were conducted using SPSS Statistics version 19 (IBM Corp., USA). All analyses were two-tailed, with significance set at $p=0.001$ to allow for the effects of multiple testing, where the number of significant findings by chance increases with the number of comparisons run. A value of $p=0.001$ was thought unlikely enough to be a chance finding (Bauer 1991).

All variables were checked for normality. Discrete variables were evaluated using the Chi-square test and continuous variables using the Student's T-test. The Mann-Whitney-U test was used for non-parametric variables. Results are presented as mean ± standard deviation for normally-distributed variables or as a median with interquartile range (IQR 25-75%) for non-normally distributed data as appropriate, or as number and percentage.

Pearson's and Spearman's rank correlations were used to explore the correlations between continuous variables, presented as Pearson's r and p-value or Spearman's ρ and p-value as appropriate.

Regression analysis was undertaken to explore significant associations between variables, using binary logistic regression (reported as odds ratio (OR) with 95% confidence interval (CI)) for categorical variables and generalised linear modelling (reported as β-coefficient with 95% CI) for continuous variables. Variables of interest generated by exploration were entered into the appropriate regression model, with the least significant variables then removed from the model in a stepwise fashion. Age and gender were allowed to remain in the model, even if non-significant, to control for the effect of these variables, which are known to be significant risk factors for OSAHS (see Section 2.3.1). Where a significant gender difference was noted during exploration, regression/modelling was conducted separately for each gender rather than by adjusting for gender to avoid possible interaction effects.

5.2 Results

Of 5270 questionnaires sent to adults with DS across the UK (74% England, 14% Scotland, 5% Wales, 7% Northern Ireland), 1321 responses were received (25%). A summary of study participation is shown in Figure 17. The proportion of responses received after initial and subsequent waves of contact are summarised in Table 4.

Of the responses received, 1105 (21%) were valid for analysis (see Figure 17). The overall valid response rate excluding participants on CPAP was 20% (England 19%,

Scotland 37%, Wales 17%, Northern Ireland 15%). When compared with the average population distribution of the UK during the period of the study (Office for National Statistics 2013; Office for National Statistics 2014), England appears to be under-represented in our sample (66% of responses v. 84% of UK population), whilst Scotland is over-represented (25% v. 8%). The percentage of responses received from participants in Wales and Northern Ireland were broadly representative (4% v. 4%, 5% v. 3% respectively).

5.2.1 Anthropometric data

The anthropometric characteristics of all remaining valid questionnaire responders (n=1067) are shown in Table 5.

There was an even gender split (54.8% males, 45.0% females; 2 responders did not state gender). Females had a significantly higher BMI than males (males 28.2±6.6kg/m^2, females 30.0±6.8kg/m^2; $p<0.0001$), although collar size was larger in males than females (males 41.3±3.8cm, females 38.2±4.5cm; $p<0.0001$). No other significant gender differences were observed.

Responders were primarily young adults who were overweight (34%) or obese (40%) according to the World Health Organisation BMI classification (World Health Organization 2006). WHO BMI categories are only valid for individuals aged ≥20 years, and as such were reported for 70% of our cohort.

There was a significant correlation between BMI and collar size ($r=0.533$, $p<0.0001$). Weak but significant associations between age and BMI ($r=0.137$, $p<0.0001$), and age and collar size ($r=0.179$, $p<0.0001$) were also noted.

Seven percent of responders reported a formal diagnosis of OSA (53 males, 28 females). Of these, just under half (38 responders) reported that they were receiving treatment with continuous positive airway pressure (CPAP) therapy and were excluded from further analysis. Other reported sleep disorders included insomnia (n=2), narcolepsy (n=1), behavioural sleep problems (n=1), parasomnia (n=1), headbanging (n=1), myoclonic jerks (n=1), nightmares (n=1) and somniloquy (n=1).

Figure 17: CONSORT diagram detailing questionnaires distributed, returned and analysed.

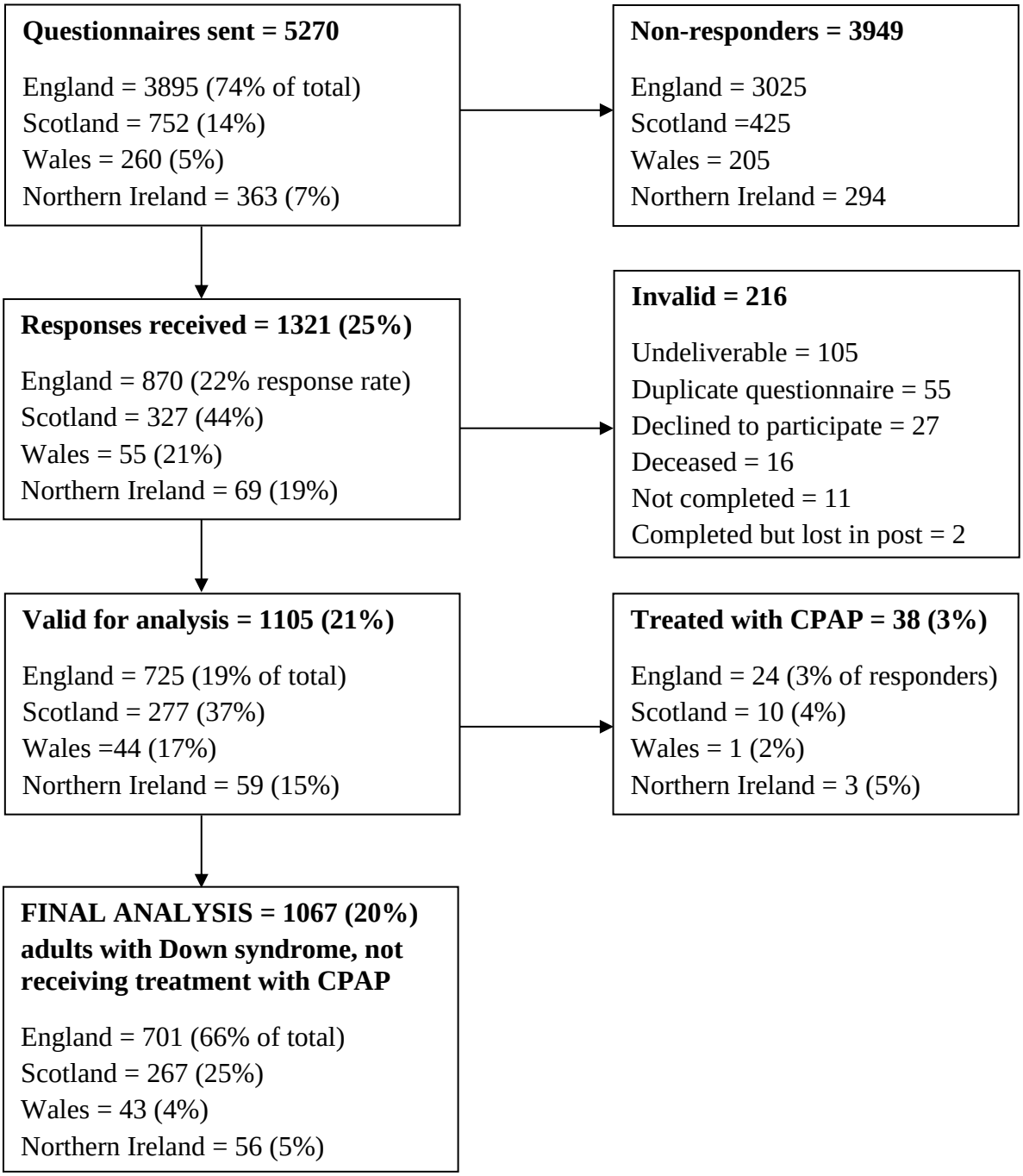


Table 4: Summary of questionnaire distribution by different organisations, including number of questionnaires received in initial and subsequent waves of distribution.

*** Second questionnaire sent by all except DS Scotland, who sent a reminder email.**

**** Second questionnaire.**

Organisation	Total sent	Responses wave 1	Responses wave 2 *	Responses wave 3 **	Total responses received
Down's Syndrome Association	4019	809	-	-	809
Down's Heart Group	521	128	55	-	183
Down's Syndrome Scotland	450	64	112	35	211
Greater Glasgow & Clyde Primary Care Group	142	44	21	-	65
Department of Sleep Medicine, Royal Infirmary of Edinburgh	98	37	6	-	43
Sleep Scotland	17	2	3	-	5
Other	23	3	2	-	5
TOTAL	**5270**	**1087**	**199**	**35**	**1321**
Response rate %	**-**	**20.6%**	**3.8%**	**0.7%**	**25.1%**

5.2.2 Comorbidities

Reported comorbidities are summarised in Table 6.

Heart problems and thyroid problems were common (37% and 36% respectively), and occurred significantly more frequently in females (heart 31% males, 45% females; thyroid 29% of males, 44% of females; both $p<0.0001$). No other gender differences were evident. Prevalence of other comorbidities potentially related to OSA or affecting sleep was low: hay fever (18%); asthma (13%); epilepsy (6%); diabetes (3%); hypertension (2%); stroke (2%).

5.2.3 Sleep symptoms

Self-reported sleep and behaviour characteristics are summarised in Table 6.

Males were significantly sleepier than females (p=0.02), although mean ESS scores across the cohort were within the normal range (7±5; scores of >10 are consistent with excessive daytime somnolence (EDS), and scores ≤10 are considered normal). Overall, 23% of responders were classified as having EDS on the pESS (no significant gender difference), although 11% did not complete the pESS.

Overall, the mean self-reported total sleep time (TST) was 9.1±1.3hr in 24hr, with 8.6±1.2hr nocturnal sleep. The majority of participants (72%) did not nap in the daytime. Of those participants reporting daytime napping, 8% napped for <1hr, 18% napped for 1-3 hours and 2% napped for >3hr per day. TST in 24hr and nocturnal TST were significantly higher in females (8.9±1.4hr males, 9.2±1.3hr females, p=0.004; 8.5±1.3hr males, 8.8±1.2hr females, <0.0001). There was no significant gender difference in the estimated duration of daytime naps.

No significant gender differences were observed in the reporting of symptoms of SDB, including snoring, witnessed apnoeas, nocturnal choking, unrefreshing sleep, frequent night wakenings and daytime sleepiness. Snoring was reported by 830 responders (79%); with snoring occurring frequently (≥3 nights per week) in 434 (41%). Apnoeas were witnessed in 309 participants (30%); frequent apnoeas in 149 (15%). Unrefreshing sleep was noted in 760 participants (73%); frequent unrefreshing sleep in 332 (32%). Daytime sleepiness was reported by 787 participants (75%); 287 (27%) reporting this frequently. Over a third of respondents (34%) did not know whether or not they had witnessed apnoeas, much higher than compared with the other sleep symptoms (7% snoring, 10% choking, 6% night wakenings, 7% unrefreshing sleep, 2% daytime sleepiness).

When assessed for probable OSAHS using the French algorithms (Fuhrman et al. 2012), 366 (35%) of responders met the criteria for probable OSAHS on ≥1 of the three algorithms (henceforth referred to as “probable OSAHS”).

The characteristics of those with probable OSAHS are summarised in Table 8. Responders with probable OSAHS were significantly younger, had a higher BMI, higher mean total pESS and were more likely to have pESS>10 (all p<0.0001).

Although TST overall was similar between those with probable OSAHS and those without (p=0.10), the distribution of TST across the day differed, with significantly longer daytime naps (p<0.0001) and shorter nocturnal sleep (p=0.02) in those with probable OSAHS. Snoring, witnessed apnoeas, nocturnal choking episodes, night awakenings, unrefreshing sleep and daytime sleepiness were all significantly more common in those with probable OSAHS (all p<0.0001). All of the probable OSAHS group were frequent snorers (this was a common variable in all 3 algorithms), in contrast to 67.0% of the group where OSAHS was not suspected.

Total pESS was significantly associated with longer TST in 24hr (r=0.206, p<0.0001), longer daytime TST (ρ=0.549, p<0.0001) and, inversely, with nocturnal TST (r=-0.131, p<0.0001). Total pESS was also associated with BMI (r=0.220, p<0.0001), collar size (r=0.180, p<0.0001) and, weakly, with age (r=0.077, p=0.02). Weak inverse correlations were noted between nocturnal TST and age (r=-0.066, p=0.04), and nocturnal TST and collar size (r=-0.104, p=0.01). BMI was associated with increased daytime TST (ρ=0.198, p<0.0001) and weakly associated with increased TST in 24hr (r=0.096, p=0.04). Daytime TST was also weakly but significantly associated with age (ρ=0.091, p=0.009) and collar size (ρ=0.120, p=0.009).

Determinants of pESS, EDS and probable OSAHS were explored using regression analysis and the results summarised in Table 9a/b. For pESS, age, BMI, hay fever, category G and N medications, and pause frequency remained in the model after stepwise forward selection, of which all but age were significant. Witnessed apnoeas were the most significant determinant of pESS score, with apnoeas seen 1-2 nights/week giving an OR of 2 (CI 0.8-2.8, p=0.001) and ≥3 nights per week increasing the OR to 6 (CI 4.4-6.6, p<0.0001). Witnessed apnoeas also predicted a small but significant increase in likelihood of EDS (OR 0.3, CI 0.2-0.6, p<0.0001).

Use of neurological drugs was associated with a higher pESS score (OR 2.0, CI 0.8-3.1, p=0.001) and EDS (OR 0.1, CI 0.1-0.2, p<0.0001). Use of respiratory medications was a small but significant determinant of probable OSAHS (OR 0.6, CI 0.4-0.9, p=0.01). Category G drugs (genito-urinary and sex hormones), were

associated with a doubling in chance of higher pESS scores (OR 2.2, CI 0.5-3.9, p=0.01).

BMI was a significant determinant of higher pESS score (OR 0.1, CI 0.0-0.2, p=0.004) and probable OSA (OR 1.1, CI 1.1-1.1, p<0.0001), but did not predict EDS. Hay fever and epilepsy were the only comorbidities predicting sleepiness or OSAHS, with small but significant increases in likelihood noted for increased pESS score (OR 1.3, CI 0.2-2.4, p=0.02) and probable OSAHS (OR 0.2, CI 0.1-0.5, p<0.0001) respectively.

5.2.4 Behavioural and emotional disturbances

Gender differences in behaviour are summarised in Table 6. Females had significantly higher raw (p=0.003) and mean (p=0.002) Disruptive scale scores and exhibited a wider range of Disruptive behaviours (p=0.001), although the intensity of behaviour did not differ significantly from males (p=0.55). A floor effect was observed in the Anxiety/Antisocial subscale, with very low mean responses reported. No significant gender differences were noted. No significant gender differences were apparent in terms of the intensity of Depressive behaviours or raw scores, although women had higher mean scores (p=0.04) and checked more behaviours (p=0.03) than men.

Those with probable OSAHS scored significantly higher on all three DBC-A domains, at all 4 scoring levels (all p<0.0001, except: Anxiety/Antisocial SIS p=0.047, II p=0.001; Depressive II p=0.002) – see Table 8.

Higher total pESS score was significantly associated with increased scores on all three behaviour subscales, regardless of scoring method (all p<0.0001), as was self-reported duration of daytime napping (all p<0.0001). Longer estimated TST in 24hr was weakly associated with higher Disruptive (ρ=0.147, p=0.001) and Depressive (ρ=0.118, p=0.01) SIS/MIS/PIC/II scores. BMI was weakly but significantly associated with increased Anxiety/Antisocial SIS and Depressive SIS/MIS scores. Age showed weak but significant negative associations with Disruptive scale SIS, and MIS/PIC/II in the Disruptive and Anxiety/Antisocial domains (data not shown).

The significance of sleepiness, symptoms of SDB and probable OSAHS as determinants for behavioural and emotional disturbance based on SIS was explored using regression analysis (Table 9a/b and Table 10). Determinants of Disruptive behaviour were analysed separately for men and women due to the significant difference noted in scores between genders. The decision to split the data rather than adjust for gender was made since the significantly different variables did not appear to behave in a similar manner in males and females at baseline, suggesting a possible interaction. Use of nervous system (category N) medication was a predictor of Disruptive behaviour, with men 3 times more likely (CI 1.2-4.8, p=0.001) and women 4 times more likely (CI 2.6-5.6, p<0.0001) to have higher scores in this subscale when taking these drugs. Category N medication was also a significant determinant of Depressive (OR 2.3, CI 1.6-3.0, p<0.0001), but not Anxiety/Antisocial behaviour scores (OR 0.1, CI -0.2-0.4, p=0.56).

Snoring 1-2 nights/week reduced the likelihood of Disruptive behaviour in males (OR -1.8, CI -3.4--0.1, p=0.04), but snoring did not influence scores in women or in the other subscales. Witnessed apnoeas 1-2 nights/week predicted increased Disruptive behaviour scores in men (OR 2.0, CI 0.3-3.7, p=0.02), but lower scores in women (OR -1.6, CI -3.1--0.1, p=0.04). Choking episodes did not affect Disruptive scores in men, but resulted in an OR of 3 (OR1.1-4.1, p=0.001) to 4 (OR1.0-6.7, p=0.01) in women, depending on severity of symptoms. Frequent awakenings 1-2 nights/week doubled the likelihood of higher Disruptive scores in males (OR 2.0, CI 0.3-3.7, p=0.02), with the OR increasing to 4 (CI 1.7-5.7, p<0.0001) with awakenings ≥3 nights per week, but had no significant effect in females. Unrefreshing sleep ≥3 nights per week increased the chance of higher scores on the Anxiety/Antisocial (OR 0.5, CI 0.1-1.0, p=0.03) and Depressive (OR 2.3, CI 1.4-3.3, p<0.0001) subscales. Daytime sleepiness ≥3 nights per week was associated with increased risk of Anxiety/Antisocial behaviour (OR 0.5, CI 0.1-0.9, p=0.01).

5.2.5 Medication

Self-reported medication use is detailed in Table 11 and Table 12. Medication use was frequent, reported by 63% of males and 75% of females (p=<0.0001). The

female predominance in medication use remained evident regarding the types of medication; drugs within ATC-DDD categories G (genitourinary and sex hormones), category H (systemic hormonal preparations excluding sex hormones and insulin), and category N (nervous system) were all used more frequently by females. The difference in category G drug use may be partly explained by the use of hormonal contraceptives in 62 females (13%). Females were more likely to take antidepressants (18 (3%) males, 37 (8%) females, p=0.001), classified under category N.

There were no significant differences between genders in use of medications which might have influenced sleep, including benzodiazepines/Z-drugs, antihistamines, antiepileptics, opiates or melatonin.

Responders with probable OSAHS were significantly more likely to be on medication of any type, with three-quarters using at least one drug. Those with probable OSAHS were significantly more likely to be taking drugs in categories G, N, and R (respiratory system), antihistamines and anti-epileptic medication.

5.2.6 Adenotonsillectomy

Removal of tonsils and adenoids was common, with 249 (23%) responders reporting removal of tonsils and/or adenoids and 124 (12%) reporting adenotonsillectomy. Characteristics of responders by surgery status is summarised in Table 13. Those who had undergone surgery were significantly younger, but there was no significant difference in surgery status between genders. Surgery did not result in lower mean pESS scores (8±6 v. 7±5; p=0.25), and there was no significant improvement in self-reported subjective sleepiness (p=0.18). Indeed, those who had previously undergone surgery were significantly more likely to exhibit symptoms of OSAHS, including snoring, witnessed apnoeas, nocturnal choking episodes and frequent night wakening. Participants who had undergone surgery were significantly more likely to exhibit EDS (p=0.02), with 28% scoring >10 on the pESS.

Individuals who had previously had surgery were more likely to have a formal diagnosis of OSA (7% v. 2%; p=0.04), as well as being more likely to meet the

criteria for probable OSAHS (42% v. 32%; p=0.002). Those with probable OSAHS were significantly more likely to have had adenoidectomy (23%; p=0.001), tonsillectomy (22%; p=0.01) or adenotonsillectomy (16%; p=0.001) than those in whom OSAHS was not suspected (14%, 15%, and 9% respectively).

Previous surgery was associated with higher scores on the Disruptive (p=0.04) and Depressive (p=0.02), but not Anxiety/Antisocial (p=0.22), subscales of the DBC-A.

Table 5: Anthropometric characteristics of all valid questionnaire responders, with responders on CPAP therapy excluded. Chi-square test used for parametric categorical variables, t-test for continuous categorical variables and Mann-Whitney U test for non-parametric variables. Values presented as mean±SD or n % unless otherwise stated.

*** Gender of 2 responders unknown.**

**** Difference between males and females**

***** WHO BMI category calculated for participants aged ≥20 years only**

Characteristics	Total responses	All responders n = 1067		Male n = 585 (54.8%) *		Female n = 480 (45.0%) *		p **
Age (years)	1062	28±9		28±9		28±9		0.99
Body Mass Index (kg/m^2) ***	911	29.0±6.8		28.2±6.6		30.0±6.8		<0.0001
Underweight (<18.5kg/m^2)	744	6	0.8%	3	0.7%	3	0.9%	0.001
Normal weight (18.5-24.99kg/m^2)		187	25.1%	124	30.1%	63	19.0%	
Pre-obesity (25.0-29.99kg/m^2)		255	34.3%	147	35.7%	107	32.3%	
Obesity class I (30.0-34.99kg/m^2)		154	20.7%	74	18.0%	80	24.2%	
Obesity class II (35.0-39.99kg/m^2)		91	12.2%	43	10.4%	48	14.5%	
Obesity class III (≥40.00kg/m^2)		51	6.9%	21	5.1%	30	9.1%	
Collar size (cm)	579	40.4±4.3		41.3±3.8		38.2±4.5		<0.0001
Smoking status:								
Smoker	1017	1	0.1%	1	0.2%	0	0.0%	0.54
Ex-smoker		5	0.5%	2	0.4%	3	0.6%	
Non-smoker		1011	99.4%	548	99.5%	462	99.4%	
Any medication	1067	728	68.2%	369	63.1%	359	74.8%	<0.0001
Comorbidities:								
Asthma	1067	135	12.7%	75	12.8%	60	12.5%	0.93
Stroke	1067	16	1.5%	7	1.2%	9	1.9%	0.45
Broken nose	1067	8	0.7%	6	1.0%	2	0.4%	0.31
Diabetes	1067	29	2.7%	13	2.2%	16	3.3%	0.34
Heart problems	1067	37.2	3.5%	182	31.1%	215	44.8%	<0.0001
Hay fever	1067	193	18.1%	104	17.8%	89	18.5%	0.75
Thyroid problems	1067	379	35.5%	168	28.7%	210	43.8%	<0.0001
Epilepsy	1067	62	5.8%	31	5.3%	31	6.5%	0.43
Liver problems	1067	17	1.6%	13	2.2%	4	0.8%	0.09
Hypertension	1067	19	1.8%	9	1.5%	10	2.1%	0.64
Nasal surgery	1067	15	1.4%	8	1.4%	7	1.5%	1.00
Kidney problems	1067	23	2.2%	11	1.9%	12	2.5%	0.53
Gluten intolerance	1067	61	5.7%	26	4.4%	35	7.3%	0.06
Surgery status:								
Adenoidectomy	1067	185	17.3%	103	17.6%	182	37.9%	0.87
Tonsillectomy	1067	188	17.6%	106	18.1%	182	37.9%	0.69
Adenotonsillectomy	1067	124	11.6%	73	12.5%	51	10.6%	0.39
Any adenoid and/or tonsil surgery	1067	249	23.3%	136	23.2%	113	23.5%	0.94

Table 6: Self-reported sleep and behaviour characteristics of valid questionnaire responders, with responders on CPAP therapy excluded. Chi-square test used for parametric categorical variables, t-test for continuous categorical variables and Mann-Whitney U test for non-parametric variables. Values presented as mean±SD, median(IQR) or n % unless otherwise stated.

*** Gender of 2 responders unknown.**

**** Difference between males and females**

Sleep and behaviour characteristics	Total responses	All responders n = 1067		Male n = 585 (54.8%) *		Female n = 480 (45.0%) *		p **
Developmental Behaviour Checklist for Adults (DBC-A):								
Disruptive behaviour subscale (scale range 0-34)	1050	5 (2-10)		4 (2-9)		6 (2-11)		0.003
Mean item score (possible score 0-2)	1050	0.29 (0.12-0.59)		0.27 (0.12-0.55)		0.35 (0.16-0.65)		0.002
Proportion of items checked (possible score 0-1)	1050	0.29 (0.12-0.53)		0.24 (0.12-0.47)		0.29 (0.12-0.53)		0.001
Intensity index (possible score 0-1)	920	0.00 (0.00-0.27)		0.00 (0.00-0.29)		0.00 (0.00-0.27)		0.55
Anxiety/Antisocial subscale (scale range -2-14)	1035	0 (0-1)		0 (0-1)		0 (-1-1)		0.96
Mean item score (possible score 0-2)	1035	0.22 (0.00-0.33)		0.22 (0.00-0.33)		0.22 (0.11-0.33)		0.66
Proportion of items checked (possible score 0-1)	1035	0.11 (0.00-0.33)		0.11 (0.00-0.33)		0.11 (0.11-0.33)		0.64
Intensity index (possible score 0-1)	783	0.00 (0.00-0.50)		0.00 (0.00-0.50)		0.00 (0.00-0.50)		0.91
Depressive subscale (scale range 0-18)	1050	2 (0-5)		2 (0-5)		2 (0-5)		0.17
Mean item score (possible score 0-2)	1050	0.22 (0.00-0.56)		0.22 (0.00-0.56)		0.22 (0.00-0.56)		0.04
Proportion of items checked (possible score 0-1)	1050	0.22 (0.00-0.44)		0.22 (0.00-0.44)		0.22 (0.00-0.44)		0.03
Intensity index (possible score 0-1)	735	0.00 (0.00-0.33)		0.00 (0.00-0.33)		0.00 (0.00-0.33)		0.99
Pictorial Epworth Sleepiness Scale (pESS)	954	7±5		7±6		7±5		0.02
Pictorial Epworth Sleepiness Scale score >10	954	215	22.5%	124	23.8%	90	20.9%	0.31
Estimated total sleep time (TST) in 24 hours (hr)	559	9.1±1.3		8.9±1.4		9.2±1.3		0.004
Estimated TST during night (hr)	1011	8.6±1.2		8.5±1.3		8.8±1.2		<0.0001
Estimated TST during daytime (hr)	834	0 (0-0.5)		0 (0-0.5)		0 (0-0.5)		0.96
Naps in daytime	834	235	28.2%	125	27.9%	109	28.3%	0.94
Snoring - *ever (≥1 night/week)*	1052	*830*	*78.9%*	*462*	*80.1%*	*366*	*77.4%*	-
Never		149	14.2%	75	13.0%	74	15.6%	0.41
Rarely/sometimes (1-2 night/week)		396	37.6%	224	38.8%	171	36.2%	
Often/frequent (≥3 nights/week)		434	41.3%	238	41.2%	195	41.2%	
Don't know		*73*	*6.9%*	*40*	*6.9%*	*33*	*7.0%*	-
Witnessed apnoeas - *ever (≥1 night/week)*	1029	*309*	*30.0%*	*175*	*30.8%*	*133*	*29.0%*	-
Never		370	36.0%	200	35.2%	169	36.8%	0.19
Rarely/sometimes (1-2 night/week)		160	15.5%	83	14.6%	76	16.6%	
Often/frequent (≥3 nights/week)		149	14.5%	92	16.2%	57	12.4%	
Don't know		*350*	*34.0%*	*193*	*34.0%*	*157*	*34.2%*	-

Nocturnal choking episodes - *ever (≥1 night/week)*	1042	*282*	*27.1%*	*142*	*24.9%*	*140*	*29.9%*	-
Never		656	63.0%	362	63.4%	292	62.3%	0.37
Rarely/sometimes (1-2 night/week)		221	21.2%	111	19.4%	110	23.5%	
Often/frequent (≥3 nights/week)		61	5.9%	31	5.4%	30	6.4%	
Don't know		*104*	*10.0%*	*67*	*11.7%*	*37*	*7.9%*	-
Frequent night wakenings - *ever (≥1 night/week)*	1044	*743*	*71.2%*	*393*	*68.7%*	*349*	*74.3%*	-
Never		237	22.7%	235	41.1%	101	21.5%	0.36
Rarely/sometimes (1-2 night/week)		484	46.4%	262	45.8%	222	47.2%	
Often/frequent (≥3 nights/week)		259	24.8%	131	22.9%	127	27.0%	
Don't know		*64*	*6.1%*	*44*	*7.7%*	*20*	*4.3%*	-
Unrefreshing sleep - *ever (≥1 night/week)*	1047	*760*	*72.6%*	*413*	*72.3%*	*470*	*73.0%*	-
Never		210	20.1%	114	20.0%	95	20.0%	0.90
Rarely/sometimes (1-2 night/week)		*428*	40.9%	236	41.3%	192	40.5%	
Often/frequent (≥3 nights/week)		332	31.7%	177	31.0%	154	32.5%	
Don't know		*77*	*7.4%*	*44*	*7.7%*	*33*	*7.0%*	-
Daytime sleepiness - *ever (≥1 night/week)*	1050	*787*	*75.0%*	*443*	*93.1%*	*342*	*72.5%*	-
Never		244	23.2%	121	25.4%	123	26.1%	0.11
Rarely/sometimes (1-2 night/week)		500	47.6%	276	58.0%	224	47.5%	
Often/frequent (≥3 nights/week)		287	27.3%	167	35.1%	118	25.0%	
Don't know		*19*	*1.8%*	*12*	*2.5%*	*7*	*1.5%*	-
Obstructive sleep apnoea (OSA) status:								
Prior diagnosis of OSA	1067	44	4.1%	29	5.0%	15	3.1%	0.16
Probable OSA using definition 1	1038	350	33.7%	199	34.9%	150	32.2%	0.39
Probable OSA using definition 2	1042	356	34.2%	200	35.1%	155	33.0%	0.51
Probable OSA using definition 3	1038	352	33.9%	200	35.1%	151	32.4%	0.39
Probable OSA on ≥1 definition	1039	366	35.2%	206	36.2%	159	34.0%	0.47

Table 7: Anthropometric characteristics of responders meeting criteria for probable OSAHS on ≥1 of the 3 algorithms, with responders on CPAP therapy excluded. Chi-square test used for parametric categorical variables, t-test for continuous categorical variables and Mann-Whitney U test for non-parametric variables. Values presented as mean±SD or n % unless otherwise stated.

*** Gender of 2 responders unknown.**

**** Difference between males and females**

Characteristics	Total responses	Probable OSA n = 366 (34.3%) *		OSA not suspected n = 673 (63.1%) *		p
Age (years)	1004	26±8		29±10		<0.0001
Gender (males : females)	1037	206 : 159		363 : 309		0.47
Collar size (cm)	565	41±4.6		40.1±4.0		0.02
Body Mass Index (kg/m^2) **	884	30.0±1.3		27.4±1.2		<0.0001
Underweight (<18.5kg/m^2)	721	0	0.0%	6	1.3%	<0.0001
Normal weight (18.5-24.99kg/m^2)		42	17.3%	140	29.3%	
Pre-obesity (25.0-29.99kg/m^2)		81	33.3%	168	35.1%	
Obesity class I (30.0-34.99kg/m^2)		48	19.8%	100	20.9%	
Obesity class II (35.0-39.99kg/m^2)		44	18.1%	42	8.8%	
Obesity class III (≥40.00kg/m^2)		28	11.5%	22	4.6%	
Any medication	1039	273	74.6%	473	70.3%	0.001
Benzodiazepines/Z-drugs	1039	7	1.9%	6	0.9%	0.24
Opiates	1039	6	1.6%	6	0.9%	0.36
Antidepressants	1039	21	5.7%	33	4.9%	0.56
Antiepileptics	1039	24	6.6%	19	2.8%	0.005
Antihistamines	1039	35	9.6%	36	5.3%	0.01
Contraceptives	1039	29	7.9%	33	4.9%	0.06
Melatonin	1039	7	1.9%	9	1.3%	0.60
Oxygen	1039	4	1.1%	6	0.9%	0.75
Comorbidities:						
Asthma	1039	64	17.5%	68	10.1%	0.001
Stroke	1039	1	0.3%	14	2.1%	0.03
Broken nose	1039	1	0.3%	6	0.9%	0.43
Diabetes	1039	7	1.9%	20	3.0%	0.42
Heart problems	1039	152	41.5%	231	34.3%	0.02
Hay fever	1039	79	21.6%	111	16.5%	0.04
Thyroid problems	1039	130	35.5%	242	36.0%	0.95
Epilepsy	1039	35	9.6%	25	3.7%	<0.0001
Liver	1039	2	0.5%	13	1.9%	0.10
Hypertension	1039	10	2.7%	8	1.2%	0.08
Nasal surgery	1039	6	1.6%	8	1.2%	0.58
Kidney problems	1039	13	3.6%	9	1.3%	0.02
Gluten intolerance	1039	20	5.5%	39	5.8%	0.89
Surgery status:						
Adenoidectomy	1039	84	23.0%	96	14.3%	0.001
Tonsillectomy	1039	81	22.1%	101	15.0%	0.005
Adenotonsillectomy	1039	60	16.4%	62	9.2%	0.001
Any adenoid and/or tonsil surgery	1039	105	28.7%	135	20.1%	0.002

Table 8: Sleep and behaviour characteristics of responders meeting criteria for probable OSAHS on ≥1 of the 3 algorithms, with responders on CPAP therapy excluded. Chi-square test used for parametric categorical variables, t-test for continuous categorical variables and Mann-Whitney U test for non-parametric variables. Values presented as mean±SD, median(IQR) or n % unless otherwise stated.

Characteristics	Total responses	Probable OSA n = 366 (34.3%) *		OSA not suspected n = 673 (63.1%) *		p
Prior diagnosis of obstructive sleep apnoea (OSA)	1039	31	8.5%	13	1.9%	<0.0001
DBC-A Disruptive subscale (scale range 0-34)	1023	7 (3-12)		4 (1-8)		<0.0001
Mean item score (possible score 0-2)	1023	0.42 (0.18-0.71)		0.24 (0.06-0.50)		<0.0001
Proportion of items checked (possible score 0-1)	1023	0.41 (0.18-0.59)		0.24 (0.06-0.41)		<0.0001
Intensity index (possible score 0-1)	895	0.10 (0.00-0.33)		0.00 (0.00-0.22)		<0.0001
DBC-A Anxiety/Antisocial subscale (scale range -2-14)	1021	0 (-1-2)		0 (0-1)		0.047
Mean item score (possible score 0-2)	1021	0.22 (0.11-0.44)		0.11 (0.00-0.33)		<0.0001
Proportion of items checked (possible score 0-1)	1021	0.22 (0.11-0.33)		0.11 (0.00-0.22)		<0.0001
Intensity index (possible score 0-1)	766	0.25 (0.00-0.50)		0.00 (0.00-0.50)		0.001
DBC-A Depressive subscale (scale range 0-18)	1024	3 (1-6)		1 (0-4)		<0.0001
Mean item score (possible score 0-2)	1024	0.33 (0.11-0.67)		0.11 (0.00-0.44)		<0.0001
Proportion of items checked (possible score 0-1)	1024	0.33 (0.11-0.56)		0.11 (0.00-0.33)		<0.0001
Intensity index (possible score 0-1)	718	0.00 (0.00-0.39)		0.00 (0.00-0.25)		0.002
Pictorial Epworth Sleepiness Scale (pESS)	933	9±6		6±5		<0.0001
Pictorial Epworth Sleepiness Scale score >10	933	126	38.8%	89	14.6%	<0.0001
Estimated total sleep time (TST) in 24 hours (hr)	545	9.2±1.5		9.0±1.3		0.10
Estimated TST during night (hr)	988	8.5±1.3		8.7±1.2		0.02
Estimated TST during daytime (hr)	834	0.0 (0.0-0.1)		0.0 (0.0-0.0)		<0.0001
Naps in daytime	812	111	40.8%	123	22.8%	<0.0001
Snoring - *ever (≥1 night/week)*	1038	*366*	*100.0%*	*450*	*67.0%*	-
Never		0	0.0%	149	22.2%	<0.0001
Rarely/sometimes (1-2 night/week)		0	0.0%	396	58.9%	
Often/frequent (≥3 nights/week)		366	100.0%	54	8.0%	
Don't know		*0*	*0.0%*	*73*	*10.9%*	-
Witnessed apnoeas - *ever (≥1 night/week)*	1017	*206*	*56.9%*	*103*	*15.7%*	-
Never		20	5.5%	339	51.8%	<0.0001
Rarely/sometimes (1-2 night/week)		82	22.7%	78	11.9%	
Often/frequent (≥3 nights/week)		124	34.3%	25	3.8%	
Don't know		*136*	*37.6%*	*213*	*32.5%*	-

Nocturnal choking episodes - *ever (≥1 night/week)*	1021	*160*	*44.9%*	*117*	*17.6%*	-
Never		145	40.7%	495	74.4%	<0.0001
Rarely/sometimes (1-2 night/week)		111	31.2%	105	15.8%	
Often/frequent (≥3 nights/week)		49	13.8%	12	1.8%	
Don't know		*51*	*14.3%*	*53*	*8.0%*	-
Frequent night wakenings - *ever (≥1 night/week)*	1021	*292*	*81.1%*	*434*	*65.7%*	-
Never		36	10.0%	195	29.5%	<0.0001
Rarely/sometimes (1-2 night/week)		158	43.9%	316	47.8%	
Often/frequent (≥3 nights/week)		134	37.2%	118	17.9%	
Don't know		*32*	*8.9%*	*32*	*4.8%*	-
Unrefreshing sleep - *ever (≥1 night/week)*	1027	*313*	*86.2%*	*431*	*64.9%*	-
Never		18	5.0%	188	28.3%	<0.0001
Rarely/sometimes (1-2 night/week)		118	32.5%	299	45.0%	
Often/frequent (≥3 nights/week)		195	53.7%	132	19.9%	
Don't know		*32*	*8.8%*	*45*	*6.8%*	-
Daytime sleepiness - *ever (≥1 night/week)*	1029	*322*	*88.7%*	*448*	*67.3%*	-
Never		36	9.9%	205	30.8%	<0.0001
Rarely/sometimes (1-2 night/week)		150	41.3%	335	50.3%	
Often/frequent (≥3 nights/week)		172	47.4%	113	17.0%	
Don't know		*5*	*1.4%*	*13*	*2.0%*	-

Table 9a: Determinants of sleepiness as assessed by generalised linear modelling, reported as β-coefficient with 95% CI.

Variable	Determinants remaining in model	β-coefficient	95% CI lower	95% CI upper	p
Pictorial Epworth Sleepiness Scale	Age	0.0	0.0	0.1	0.07
	BMI	0.1	0.0	0.2	0.004
	Hay fever	1.3	0.2	2.4	0.02
	Category G medication	2.2	0.5	3.9	0.01
	Category N medication	2.0	0.8	3.1	0.001
	Witnessed apnoeas - rarely/sometimes (1-2 nights/week)	1.8	0.8	2.8	0.001
	Witnessed apnoeas - often/frequently (≥3 nights/week)	5.5	4.4	6.6	<0.0001

Table 9b: Determinants of sleepiness and probable OSAHS as assessed by binary logistic regression, reported as Odds Ratio with 95% CI.

Variable	Determinants remaining in model	Odds Ratio	95% CI lower	95% CI upper	p
Excessive daytime sleepiness (pESS >10)	Age	1.0	1.0	1.1	0.14
	BMI	1.0	1.0	1.1	0.08
	Category N medication	0.4	0.2	0.7	0.001
	Witnessed apnoeas - rarely/sometimes (1-2 nights/week)	0.1	0.1	0.2	<0.0001
	Witnessed apnoeas - often/frequently (≥3 nights/week)	0.3	0.2	0.6	<0.0001
Probable obstructive sleep apnoea/hypopnoea syndrome	Age	1.0	0.9	1.0	<0.0001
	BMI	1.1	1.1	1.1	<0.0001
	Epilepsy	0.2	0.1	0.5	<0.0001
	Category R medication	0.6	0.4	0.9	0.01

Table 10: Determinants of behaviour as assessed by generalised linear modelling, reported as β-coefficient with 95% CI. . DBC-A Disruptive subscale analysed separately for males and females due to significant difference in scores at baseline (adjusting for gender inappropriate due to noted possibility of interaction effect).

Variable	Determinants remaining in model	β-coefficient	95% CI lower	95% CI upper	p
DBC-A Disruptive - Male	Category N medication	3.0	1.2	4.8	0.001
	Snoring - rarely/sometimes (1-2 nights/week)	-1.8	-3.4	-0.1	0.04
	Snoring - often/frequently (≥3 nights/week)	-1.4	-3.3	0.6	0.16
	Witnessed apnoeas - rarely/sometimes (1-2 nights/week)	2.0	0.3	3.7	0.02
	Witnessed apnoeas - often/frequently (≥3 nights/week)	1.5	-0.5	3.5	0.14
	Nocturnal choking - rarely/sometimes (1-2 nights/week)	1.4	-2.1	3.0	0.09
	Nocturnal choking - often/frequently (≥3 nights/week)	-0.4	-3.2	2.4	0.77
	Frequent awakenings - rarely/sometimes (1-2 nights/week)	1.8	0.3	3.3	0.02
	Frequent awakenings - often/frequently (≥3 nights/week)	3.7	1.7	5.7	<0.0001
	Unrefreshing sleep - rarely/sometimes (1-2 nights/week)	-0.1	-1.7	1.4	0.85
	Unrefreshing sleep - often/frequently (≥3 nights/week)	2.1	-0.2	4.3	0.07
DBC-A Disruptive - Female	Category N medication	4.1	2.6	5.6	<0.0001
	Snoring - rarely/sometimes (1-2 nights/week)	0.6	-1.0	2.2	0.47
	Snoring - often/frequently (≥3 nights/week)	0.5	-1.2	2.3	0.54
	Witnessed apnoeas - rarely/sometimes (1-2 nights/week)	-1.6	-3.1	-0.1	0.04
	Witnessed apnoeas - often/frequently (≥3 nights/week)	-0.8	-3.2	1.5	0.48
	Nocturnal choking - rarely/sometimes (1-2 nights/week)	2.6	1.1	4.1	0.001
	Nocturnal choking - often/frequently (≥3 nights/week)	3.9	1.0	6.7	0.01
	Frequent awakenings - rarely/sometimes (1-2 nights/week)	1.4	-0.1	2.9	0.08
	Frequent awakenings - often/frequently (≥3 nights/week)	-0.2	-2.1	1.7	0.85
	Unrefreshing sleep - rarely/sometimes (1-2 nights/week)	1.5	0.0	3.0	0.06
	Unrefreshing sleep - often/frequently (≥3 nights/week)	6.2	4.3	8.1	<0.0001

Variable	Determinants remaining in model	β-coefficient	95% CI lower	95% CI upper	p
DBC-A Anxiety/Antisocial	Category R medication	0.3	0.0	0.6	0.09
	Category N medication	0.1	-0.2	0.4	0.56
	Snoring - rarely/sometimes (1-2 nights/week)	0.0	-0.4	0.3	0.82
	Snoring - often/frequently (≥3 nights/week)	-0.3	-0.7	0.1	0.13
	Witnessed apnoeas - rarely/sometimes (1-2 nights/week)	0.2	-0.2	0.5	0.32
	Witnessed apnoeas - often/frequently (≥3 nights/week)	-0.1	-0.5	0.3	0.67
	Nocturnal choking - rarely/sometimes (1-2 nights/week)	0.3	0.0	0.7	0.03
	Nocturnal choking - often/frequently (≥3 nights/week)	0.5	-0.1	1.1	0.11
	Frequent awakenings - rarely/sometimes (1-2 nights/week)	0.1	-0.2	0.4	0.55
	Frequent awakenings - often/frequently (≥3 nights/week)	0.0	-0.4	0.4	0.87
	Unrefreshing sleep - rarely/sometimes (1-2 nights/week)	0.0	-0.3	0.3	1.00
	Unrefreshing sleep - often/frequently (≥3 nights/week)	0.5	0.1	1.0	0.03
	Daytime sleepiness - rarely/sometimes (1-2 nights/week)	0.2	-0.1	0.5	0.20
	Daytime sleepiness - often/frequently (≥3 nights/week)	0.5	0.1	0.9	0.01
DBC-A Depressive	Category R medication	0.0	-0.7	0.7	1.00
	Category N medication	2.3	1.6	3.0	<0.0001
	Snoring - rarely/sometimes (1-2 nights/week)	-0.2	-0.9	0.5	0.50
	Snoring - often/frequently (≥3 nights/week)	-0.2	-1.0	0.5	0.55
	Witnessed apnoeas - rarely/sometimes (1-2 nights/week)	0.4	-0.3	1.1	0.22
	Witnessed apnoeas - often/frequently (≥3 nights/week)	0.9	0.0	1.8	0.06
	Nocturnal choking - rarely/sometimes (1-2 nights/week)	0.5	-0.2	1.1	0.16
	Nocturnal choking - often/frequently (≥3 nights/week)	0.5	-0.7	1.6	0.46
	Frequent awakenings - rarely/sometimes (1-2 nights/week)	0.5	-0.2	1.1	0.15
	Frequent awakenings - often/frequently (≥3 nights/week)	0.3	-0.6	1.1	0.52
	Unrefreshing sleep - rarely/sometimes (1-2 nights/week)	0.5	-0.2	1.1	0.19
	Unrefreshing sleep - often/frequently (≥3 nights/week)	2.3	1.4	3.3	<0.0001
	Daytime sleepiness - rarely/sometimes (1-2 nights/week)	-0.1	-0.7	0.5	0.67
	Daytime sleepiness - often/frequently (≥3 nights/week)	0.5	-0.3	1.3	0.23

Table 11: Self-reported medication status of valid questionnaire responders, by gender, based on World Health Organisation Anatomical Therapeutic Chemical Classification System (WHO ATC) category. Drugs types known to affect sleep are also listed. Responders on CPAP therapy are excluded. Chi-square test used for all variables. Results presented as n % unless otherwise stated.

*** Gender of 2 responders unknown**

**** Difference between males and females with DS**

***** Includes supplementary oxygen**

WHO ATC category	Total responses	All reponders		Male		Female		p **
		n = 1067		n = 585 (54.8%) *		n = 480 (45.0%) *		
A - Alimentary tract and metabolism	1067	230	21.6%	121	20.7%	109	22.7%	0.45
B - Blood and blood forming organs	1067	40	3.7%	18	3.1%	22	4.6%	0.26
C - Cardiovascular system	1067	78	7.3%	40	6.8%	38	7.9%	0.56
D - Dermatologicals	1067	121	11.3%	74	12.6%	47	9.8%	0.15
G - Genito-urinary system and sex hormones	1067	84	7.9%	9	1.5%	75	15.6%	<0.0001
H - Systemic hormonal preparations, excluding sex hormones and insulins	1067	372	34.9%	170	29.1%	202	42.1%	<0.0001
J - Antiinfectives for systemic use	1067	17	1.6%	7	1.2%	10	2.1%	0.33
L - Antineoplastic and immunomodulating agents	1067	8	0.7%	2	0.3%	6	1.3%	0.15
M - Musculo-skeletal system	1067	44	4.1%	27	4.6%	17	3.5%	0.44
N - Nervous system	1067	197	18.5%	93	15.9%	104	21.7%	0.02
P - Antiparasitic products, insecticides and repellents	1067	0	0.0%	0	0.0%	0	0.0%	-
R - Respiratory system	1067	165	15.5%	15	2.6%	19	4.0%	0.22
S - Sensory organs	1067	34	3.2%	82	14.0%	83	17.3%	0.15
V - Various ***	1067	12	1.1%	3	0.5%	9	1.9%	0.04
Over-the-counter medications with no clear WHO ATC category	1067	72	6.7%	31	5.3%	41	8.5%	0.04
Opiates	1067	12	1.1%	5	0.9%	7	1.5%	0.39
Antidepressants	1067	55	5.2%	18	3.1%	37	7.7%	0.001
Benzodiazepines / Z-drugs	1067	13	1.2%	4	0.7%	9	1.9%	0.10
Antiepileptics	1067	44	4.1%	21	3.6%	23	4.8%	0.36
Antihistamines	1067	72	6.7%	34	5.8%	38	7.9%	0.18
Contraceptives	1067	-	-	-	-	62	12.9%	-
Oxygen	1067	11	1.0%	3	0.5%	8	1.7%	0.07
Melatonin	1067	16	1.5%	11	1.9%	5	1.0%	0.32

Table 12: Self-reported medication status of valid questionnaire responders, by probable OSAHS status, based on World Health Organisation Anatomical Therapeutic Chemical Classification System (WHO ATC) category. Drugs types known to affect sleep are also listed. Responders on CPAP therapy are excluded. Chi-square test used for all variables. Values presented as n % unless otherwise stated.

*** Gender of 2 responders unknown**

**** WHO BMI categories calculated for participants aged ≥20 years only**

WHO ATC category	Total responses	Probable OSA n = 366 (34.3%) *		OSA not suspected n = 673 (63.1%) *		p
A - Alimentary tract and metabolism	1039	77	21.0%	148	22.0%	0.75
B - Blood and blood forming organs	1039	14	3.8%	26	3.9%	1.00
C - Cardiovascular system	1039	22	6.0%	54	8.0%	0.26
D - Dermatologicals	1039	48	13.1%	71	10.5%	0.22
G - Genito-urinary system and sex hormones	1039	40	10.9%	44	6.5%	0.02
H - Systemic hormonal preparations, excluding sex hormones and insulins	1039	129	35.2%	235	34.9%	0.95
J - Antiinfectives for systemic use	1039	8	2.2%	9	1.3%	0.31
L - Antineoplastic and immunomodulating agents	1039	5	1.4%	3	0.4%	0.14
M - Musculo-skeletal system	1039	19	5.2%	23	3.4%	0.19
N - Nervous system	1039	85	23.2%	108	16.0%	0.01
P - Antiparasitic products, insecticides and repellents	1039	0	0.0%	0	0.0%	-
R - Respiratory system	1039	77	21.0%	86	12.8%	0.001
S - Sensory organs	1039	10	2.7%	22	3.3%	0.71
V - Various **	1039	5	1.4%	6	0.9%	0.53
Over-the-counter medications with no clear WHO ATC category	1039	27	7.4%	42	6.2%	0.52
Opiates	1039	6	1.6%	6	0.9%	0.36
Antidepressants	1039	21	5.7%	33	4.9%	0.561
Benzodiazepines / Z-drugs	1039	7	1.9%	6	0.9%	0.24
Antiepileptics	1039	24	6.6%	19	2.8%	0.01
Antihistamines	1039	35	9.6%	36	5.3%	0.01
Contraceptives (% of females)	1039	29	18.4%	33	10.7%	0.06
Oxygen	1039	4	1.1%	6	0.9%	0.75
Melatonin	1039	7	1.9%	9	1.3%	0.60

Table 13: Self-reported sleep and behaviour characteristics of valid questionnaire responders by surgery status, with responders on CPAP therapy excluded. Chi-square test used for parametric categorical variables, t-test for continuous categorical variables and Mann-Whitney U test for non-parametric variables. Values presented as mean±SD, median(IQR) or n % unless otherwise stated.

***OSAHS probability could not be calculated for 28 responders (2.6%)**

Anthropometric, sleep and behaviour characteristics	Total responses	TA Surgery n = 249 (23.3%)		No TA surgery n = 818 (76.7%)		p
Age (years)	1062	26±8		28±10		0.002
Gender (males : females)*	1065	136 : 113		449 : 367		0.94
Body Mass Index (kg/m^2) **	911	29.4±7.0		28.9±6.7		0.24
Underweight (<18.5kg/m^2)	744	0	0.0%	6	1.1%	0.43
Normal weight (18.5-24.99kg/m^2)		51	29.3%	135	23.7%	
Pre-obesity (25.0-29.99kg/m^2)		53	30.5%	195	34.2%	
Obesity class I (30.0-34.99kg/m^2)		34	19.5%	118	20.7%	
Obesity class II (35.0-39.99kg/m^2)		21	12.1%	68	11.9%	
Obesity class III (≥40.00kg/m^2)		14	8.0%	37	6.5%	
Collar size (cm)	579	41.0±4.1		40.3±4.3		0.11
Developmental Behaviour Checklist for Adults (DBC-A):						
Disruptive behaviour subscale (scale range 0-34)	1050	6 (2-11)		5 (2-10)		0.04
Mean item score (possible score 0-2)	1050	0.35 (0.18-0.65)		0.29 (0.12-0.59)		0.01
Proportion of items checked (possible score 0-1)	1050	0.29 (0.18-0.53)		0.29 (0.12-0.47)		0.01
Intensity index (possible score 0-1)	920	0.00 (0.00-0.33)		0.00 (0.00-0.25)		0.07
Anxiety/Antisocial subscale (scale range -2-14)	1035	0 (0-1)		0 (0-1)		0.22
Mean item score (possible score 0-2)	1035	0.22 (0.11-0.44)		0.22 (0.00-0.33)		0.03
Proportion of items checked (possible score 0-1)	1035	0.22 (0.11-0.33)		0.11 (0.00-0.25)		0.03
Intensity index (possible score 0-1)	783	0.00 (0.00-0.50)		0.00 (0.00-0.50)		0.08
Depressive subscale (scale range 0-18)	1050	2 (1-5)		2 (0-5)		0.02
Mean item score (possible score 0-2)	1050	0.22 (0.11-0.67)		0.22 (0.00-0.56)		0.02
Proportion of items checked (possible score 0-1)	1050	0.22 (0.11-0.56)		0.22 (0.00-0.44)		0.02
Intensity index (possible score 0-1)	735	0.00 (0.00-0.38)		0.00 (0.00-0.33)		0.30
Pictorial Epworth Sleepiness Scale (pESS)	954	8±6		7±5		0.002
Pictorial Epworth Sleepiness Scale score >10	954	62	28.3%	153	20.8%	0.02
Estimated total sleep time (TST) in 24 hours (hr)	559	9.0±1.3		9.1±1.4		0.42
Estimated TST during night (hr)	1011	8.6±1.3		8.6±1.2		0.76
Estimated TST during daytime (hr)	834	0 (0-0.5)		0 (0-0.5)		0.87
Naps in daytime	834	53	27.5%	182	28.4%	0.86

Snoring - ever (≥1 night/week)	1052	208	84.6%	622	77.2%	-
Never		24	9.8%	125	15.5%	0.004
Rarely/sometimes (1-2 night/week)		85	34.6%	311	38.6%	
Often/frequent (≥3 nights/week)		123	50.0%	311	38.6%	
Don't know		14	5.7%	59	7.3%	-
Witnessed apnoeas - ever (≥1 night/week)	1029	102	43.0%	207	26.1%	-
Never		72	30.4%	298	37.6%	<0.0001
Rarely/sometimes (1-2 night/week)		44	18.6%	116	14.6%	
Often/frequent (≥3 nights/week)		58	24.5%	91	11.5%	
Don't know		63	26.6%	287	36.2%	-
Nocturnal choking episodes ever (≥1 night/week)	1042	83	34.3%	199	24.9%	-
Never		139	57.4%	517	64.6%	0.02
Rarely/sometimes (1-2 night/week)		64	26.4%	157	19.6%	
Often/frequent (≥3 nights/week)		19	7.9%	42	5.3%	
Don't know		20	8.3%	84	10.5%	-
Frequent night wakenings - ever (≥1 night/week)	1044	186	76.2%	557	69.6%	-
Never		49	20.1%	188	23.5%	0.01
Rarely/sometimes (1-2 night/week)		106	43.4%	378	47.3%	
Often/frequent (≥3 nights/week)		80	32.8%	179	22.4%	
Don't know		9	3.7%	55	6.9%	-
Unrefreshing sleep - ever (≥1 night/week)	1047	195	80.2%	565	70.3%	-
Never		34	14.0%	176	21.9%	0.002
Rarely/sometimes (1-2 night/week)		98	40.3%	330	41.0%	
Often/frequent (≥3 nights/week)		97	39.9%	235	29.2%	
Don't know		14	5.8%	63	7.8%	-
Daytime sleepiness - ever (≥1 night/week)	1050	192	79.0%	595	73.7%	-
Never		49	20.2%	195	24.2%	0.18
Rarely/sometimes (1-2 night/week)		115	47.3%	385	47.7%	
Often/frequent (≥3 nights/week)		77	31.7%	210	26.0%	
Don't know		2	0.8%	17	2.1%	-
Obstructive sleep apnoea (OSA) status:						
Prior diagnosis of OSA	1067	24	9.6%	20	2.4%	0.04
Probable OSA on ≥1 definition	1039	105	42.2%	261	31.9%	0.002

5.3 Discussion

This is the first large-scale prevalence study of OSAHS in adults with DS. Based on self-reported symptoms categorised using the French algorithms (Fuhrman et al. 2012), the prevalence of OSAHS in this population of UK adults with DS is approximately 35%. This is significantly higher than the 2-4% prevalence reported in the general population (Young et al. 1993). There was no gender difference in OSAHS prevalence in young adults with DS.

A mean prevalence of 35% is modest in comparison with the >80% quoted in previous prevalence studies for the DS population (Resta et al. 2003; Trois et al. 2009). Although both of these studies used polysomnography to collect objective prevalence data, participant numbers were small. Resta et al included only 6 participants, recruited from a single residential home. Similarly to our study, Trois et al recruited via local DS associations and clinics; however, only 16 adults with DS were included. A large population-based cohort study of adults with intellectual disability in the west of Scotland (n=1023, including 186 with DS) examined subjective prevalence of sleep problems (Boyle et al. 2010). Of 87 responders with DS, problems initiating and maintaining sleep were reported by 7-9%, but symptoms of SDB/OSAHS were not assessed. A further questionnaire study in Canada (Virji-Babul et al. 2007) found that 19-23% of 59 adults with DS enrolled with a voluntary national register of people with DS had been diagnosed with a sleep disorder by a clinical psychologist. However, the precise nature of these sleep disorders is not stated. OSA was reported by 21% of the whole group (n=223), but this included participants aged 1 month to >40 years and prevalence data for adults was not reported.

5.3.1 Anthropometric Data

Study participants ranged in age from 16 to 65 years, although the majority (69%) were aged between 20 and 40 years. The paucity of older responders may be related to a number of factors including increased risk of early-onset Alzheimer's-type dementia noted in adults with DS after age 50 (Lai & Williams 1989) and the generally reduced life expectancy (mean 51 years, median 58 years) in this

population (Wu & Morris 2013). Older adults with DS may be more likely to live in residential care, or less likely to have a living relative to assist with questionnaire completion.

The majority of participants in this study were overweight or obese, with females significantly heavier than males. Interestingly, the level of obesity in males was the same as that of the general population (24%), whilst 36% of females with DS were obese in comparison to 25% in the general population (Moody 2014). These observations support previous studies in DS and ID populations (Melville et al. 2005; Melville et al. 2007).

A number of factors may contribute to the raised mean BMI in women with DS. Females were significantly more likely to be on medication of any type, including antidepressants (8%) and hormonal contraceptives (13%) which are known to be associated with weight gain (Blumenthal et al. 2014). Thyroid problems were also significantly more prevalent in females (44%). Changes in thyroid function are associated with fluctuations in body weight. In our study, thyroid problems were significantly more prevalent in females (44%). Interestingly, a recent study in the general population in Greece demonstrated a significant link between thyroid function in BMI in women, but not men (Milionis & Milionis 2013). Thyroid dysfunction may be a contributor to the increased BMI in this group, although further investigation is required.

5.3.2 Comorbidities

Prevalence of comorbidities potentially related to OSAHS or potentially affecting sleep was generally in line with that reported in the general population and previous studies in the DS population. One paper (Upton et al. 2000) estimated the prevalence of hay fever and asthma in the UK as 20% and 8% respectively, and similar rates are noted in this study (18% and 13% respectively). Six percent of our cohort reported epilepsy, similar to previous studies in DS (9%) (McVicker et al. 1994), but much higher than the general population (<1%) (Forsgren et al. 2005). The prevalence of diabetes in the general population is estimated at 3% (Wild et al. 2004), also reflected in our study (3%). A study in the Netherlands reported hypertension in

17% of a cohort of adults with ID, however none of the subset of participants with DS were hypertensive (van de Louw et al. 2009). Unsurprisingly, hypertension was noted in only 2% of our cohort. Stroke is generally rare in young adults (<1%) (Smajlovic & Smajlović 2015), and this was again reflected in our data in young adults with DS (1%).

Participants with probable OSAHS were more likely to have asthma, heart problems, hay fever, epilepsy or kidney problems than those with low probability of OSA. This may be a reflection of sleep disturbance caused by these disorders, or the contribution of such disorders to the aetiology of OSAHS. Further investigation is warranted.

5.3.3 Sleep symptoms

A discrepancy was noted between self-reporting of daytime sleepiness per se (74%; 27% frequently) with the percentage of those reporting EDS via the pESS (20%). Although the pESS appears to be a useful measure in this population, overall scores may be reduced due to unsuitability of some of the questions. Particularly, the question relating to sitting down and reading may not be appropriate given the levels of diminished literacy in this population, and may be problematic in those with visual impairment, common in DS. In this study, over 70% of respondents noted that they did not nap during the daytime despite 20% exhibiting EDS. This may reflect a lack of opportunity to nap (due to employment, education or other daytime commitments) rather than absence of sleepiness. Modification of the pESS to improve its utility in this specific population may be appropriate and is an area for further investigation.

A large percentage of responders did not know whether or not they had apnoeas, which may have resulted in underestimation of the prevalence of this symptom. This may reflect the relative complexity of the description (people are generally more familiar with snoring than “pauses in breathing”), but may also relate to the availability of a second individual to witness the apnoeas; many people with DS live in supported accommodation without a live-in carer or family member and, whereas snoring may be heard outside the bedroom, apnoeas are not. This may also explain

the relatively young mean age of respondents, who may still reside at home. Information on living arrangements was not recorded in this study.

It should be noted that all responders with probable OSAHS reported snoring ≥3 nights per week, as this variable was common to all three algorithms. Sleep apnoea without snoring is rare in the literature, though one polysomnographic study in adults with DSDS (Andreou et al 2002) noted snoring in only 7 of 12 participants with studies diagnostic of sleep apnoea. The algorithms used in the current study may result in under-estimation of prevalence of OSAHS by excluding those who snore <3 nights per week.

5.3.4 Behavioural and emotional disturbances

Generally, scores on the subscales of the DBC-A were low. A floor effect was noted on the Anxiety/Antisocial subscale, with mean scores of 0/14 in both males and females, regardless of sleep symptoms, and those with and without probable OSAHS. There may be an element of selection bias, with families of individuals with more severe behavioural and emotional problems less likely to respond. However, probable OSAHS was associated with a significant increase in raw and mean scores as well as breadth and intensity of problem behaviours in all 3 subscales, supporting the hypothesis of SDB impacting negatively on behaviour and emotion in adults with DS.

Cognitive and behavioural deficits in adults and children with untreated SDB are well documented in the general adult population, as is reversal of these deficits with treatment (Engleman et al. 1994; Engleman et al. 1997; Engleman 1999; Engleman & Douglas 2004). Beebe and Gozal (Beebe & Gozal 2002) proposed that the neurocognitive deficits associated with untreated SDB can be explained by dysfunction of the prefrontal cortex, leading to impairment of daytime function in a range of areas including attention, motivation, control of emotion and decision-making. Since adults with DS already exhibit impairment in this and other brain regions (as discussed in Chapter 1), untreated SDB may present a “double-hit” on cognition in these individuals. It is possible that untreated SDB may contribute to acceleration of the cognitive decline seen in early-onset dementia, which is common

in adults with DS (Lai & Williams 1989; Holland et al. 1998); a recent review by Fernandez and Edgin suggests that sleep disruption might lead to both earlier onset of dementia and more rapid deterioration (Fernandez & Edgin 2013).

Breslin et al (Breslin et al. 2014) reported a 9-point IQ deficit in children with SDB and DS versus controls. Marcus et al (Marcus et al. 2012) showed an improvement in behaviour scores in subset of 10 children with neurodevelopmental disability (6 with DS) with CPAP use. However, to date, no published studies have investigated the effect of SDB on cognitive function in adults with DS, or the effect of CPAP therapy in this group.

5.3.5 Medication

High rates of medication use were reported, with 75% of those with probable OSAHS using at least one medication. Untreated OSAHS may have health economic implications in terms of prescription rates (Jennum & Kjellberg 2011), but, in this population, may also reflect the increased number of comorbidities related to DS.

5.3.6 Adenotonsillectomy

Adenotonsillectomy is the first-line treatment for OSAHS in the majority of typically-developing children, curative in 75-100% (Schechter 2002). However, less favourable results are reported in children with DS, with 30-73% exhibiting residual OSAHS despite adenotonsillectomy (Donnelly et al. 2004; Shete et al. 2010).

In this study, previous surgery did not result in a lower rate of EDS, and those who had previously had adenoids and/or tonsils removed were more likely to exhibit symptoms of OSAHS and Disruptive and Depressive behaviour. Whilst surgery may result in a partial or initial improvement, the multifactorial nature of the aetiology of OSAHS in individuals with DS must be borne in mind; multiple factors mean results are not sustained into adulthood in the DS population (Donnelly et al. 2004; Shott & Donnelly 2004). This is supported by Capone et al, who noted that prior tonsillectomy was not associated with presence or absence of OSAHS in a population of adolescents and young adults (age 14-30 years) with DS (Capone et al. 2013). However, an element of selection bias may be present, with families who

have previously had a child diagnosed with OSAHS and treated via adenotonsillectomy more likely to complete and return a questionnaire, and more vigilant regarding the recurrence of symptoms of OSAHS.

5.3.7 Limitations

Limitations of this work include the subjective nature of the study. Inherent non-responder bias in questionnaire studies is well-documented, and difficult to avoid (Pannucci & Wilkins 2010), however we believe that the questionnaire was designed in such a way as to minimise this. An element of selection bias may be evident, with those individuals and families with concerns about sleep more likely to respond.

There was some regional variation in methodology. An England-based charity which sent out the majority (3895; 74%) of the questionnaires declined to send out a second questionnaire to individuals who did not respond initially. A repeat mailout was conducted by all other services involved in the study. This may have contributed to the reduced response rate in England, Wales and Northern Ireland. Making contact a second time has been shown to increase response rates by ~20% in other studies (Hoffman et al. 1998; Nakash et al. 2006).

Although the questionnaire was designed to be completed by the individual with DS, it is likely that a large proportion of the questionnaires were completed by a proxy on the participant's behalf. A "proxy effect" has been reported in the literature (Tennant et al. 1991). However, since this more often results in under-reporting of characteristics, it is likely that our estimates of prevalence, sleepiness and behaviour are conservative.

The majority of participants were identified through patient support groups, and so may not be representative of the DS population as a whole. Older adults may be under-represented, possibly due to inability to complete the questionnaire on account of comorbidities such as dementia, or absence of a living relative or family member to assist with completion.

Information on ethnicity was not collected, and so our prevalence data may not be transferable to other countries with divergent ethnicity. However, comparison of the prevalence of OSAHS in adults with DS in Scotland with that in Japan, as discussed in Chapter 6, showed similar prevalence of symptoms despite the ethnic and anthropometric differences between these two populations (Sawatari et al. 2013).

This questionnaire focussed only on symptoms of SDB/OSAHS. However, a number of symptoms such as EDS, unrefreshing sleep and frequent night wakenings are common to other sleep disorders, and circadian rhythm disorders, insomnia or parasomnias cannot be ruled out as co-morbid or alternative causes for these symptoms.

Building on this work, obtaining objective sleep study data would further quantify the severity of SDB in adults with DS. This forms the basis of our further study, described in Chapter 7.

5.4 Conclusion

In conclusion, this first large-scale study of OSAHS prevalence in adults with DS showed an estimate of 35% – nearly 9 times higher than in the general adult population. Unfortunately, neither assessment nor treatment of OSAHS appears to be commonplace in this population clinically - as evidenced by only 7% of the study population having a prior diagnosis of OSA and only 3% receiving CPAP treatment - despite the potential benefits for improved cognitive function, health and wellbeing. This study provides evidence for advocating for improved guidelines for monitoring of SDB/OSAHS in DS adults and potentially specialised clinics or services for adults with DS and other forms of ID. In the UK, there is currently a dearth of such services, with poor transitioning from paediatric services to adult care being commonplace. Screening of adults with DS for SDB is recommended, as are measures to improve awareness of this disorder amongst people with DS, their families and all professionals involved in their care.

Chapter 6: Subjective prevalence of OSAHS in the UK and Japan – a comparative study

This study was a collaboration between our team in Edinburgh and a group of researchers from Kyushu University, Fukuoka, Japan (see Acknowledgements). This new collaboration was formed as a result of networking during the European Society of Sleep Technologists meeting in Paris in 2012, at which early results of the study described in Chapter 5 were presented (see Appendix 4).

Sleep-disordered breathing has been the subject of interethnic comparison in a number of studies in the general population. Though anatomical differences in craniofacial structure can predispose to SDB (Cistulli 1996), this is further exacerbated by differing ethnicity (Villaneuva et al. 2005). To our knowledge, there have been no studies comparing the effects of ethnicity on OSAHS prevalence in DS.

We hypothesised that the presence of DS may supercede the effect of ethnicity as a risk factor for OSAHS. Therefore, the aim of this study was to compare the prevalence of self-reported OSAHS in adults with DS in two nations with differing ethnicity - Scotland and Japan.

6.1 Methods

A comparative study was conducted using subsets of data from two cross-sectional studies conducted contemporaneously in Scotland (See Chapter 5) and Japan (Sawatari et al. 2015). Both studies received individual ethical approval from the relevant local research ethics body (Scotland A Research Ethics Committee; Ethics Committee of the Faculty of Medicine at Kyushu University, Japan, and Japan Down Syndrome Society). Written informed consent was not required, with return of a completed questionnaire considered implicit consent to participate.

In Scotland, easy-read questionnaires were sent to adults aged ≥16 years with DS and their caregivers between February 2011 and June 2014 as part of a wider study across the UK, as described in detail in Chapter 5. In Japan, questionnaires were sent

to children and adults with DS and their caregivers between May 2011 and September 2013. All individuals were members of the Japan Down Syndrome Society. Since the Japanese questionnaire surveyed both adults and children, responders aged <16 years were excluded from the comparison study analysis.

Questionnaires were completed by either the individual with DS themselves or their caregiver, dependent upon ability. Both questionnaires captured basic anthropometric data, along with more focussed questions on sleepiness and symptoms of OSAHS. Body mass index (BMI) was calculated from weight and height provided in the questionnaire, and classified according to standard classifications for overweight and obesity (World Health Organization 2006). Although alternative cut-off values have been proposed to control for differing body fat compositions between European and Asian populations (Wang et al. 1994), a World Health Organization expert review recommended that the standard cut-offs should be retained as the international classification, but with additional points included to facilitate international comparison (World Health Organization 2004).

Subjective sleepiness was rated using the pictorial Epworth Sleepiness Scale (Ghiassi et al. 2010) in English, or the Japanese version of the Epworth Sleepiness Scale (Takegami et al. 2009) as appropriate (referred to henceforth as (p)ESS). Symptoms of OSAHS (snoring, witnessed apnoeas, frequent night awakening and daytime sleepiness) were classified as occurring frequently (5–7 nights/week), sometimes (1–4 nights/week) or never (<1 night/week).

Likely diagnosis of OSAHS was determined using previously published algorithms which have been used in both the general population (Fuhrman et al. 2012) and adults with DS (see Chapter 5):

1. Frequent snoring + (witnessed apnoeas ≥1 night/week or (p)ESS>10)
2. Frequent snoring + (witnessed apnoeas ≥1 night/week or daytime sleepiness ≥1 night/week)

6.1.1 Analysis

Standard statistical analyses were undertaken using SPSS Statistics 19, (IBM Corp., USA). Analysis was conducted independently by the investigators in Scotland and Japan using a combined SPSS database of subsets of data from both studies.

Significance was set at $p<0.05$ and all analyses were two-tailed. All variables were checked for normality. The Chi-square test was used for normally-distributed discrete variables, Student's t-test for normally-distributed continuous variables, and Mann-Whitney-U test for non-normally distributed data. Results are presented as mean ± standard deviation for normal variables, or as number and percentage.

Pearson's rank correlations were used to explore associations between continuous variables, with results shown as Pearson's r and p-value.

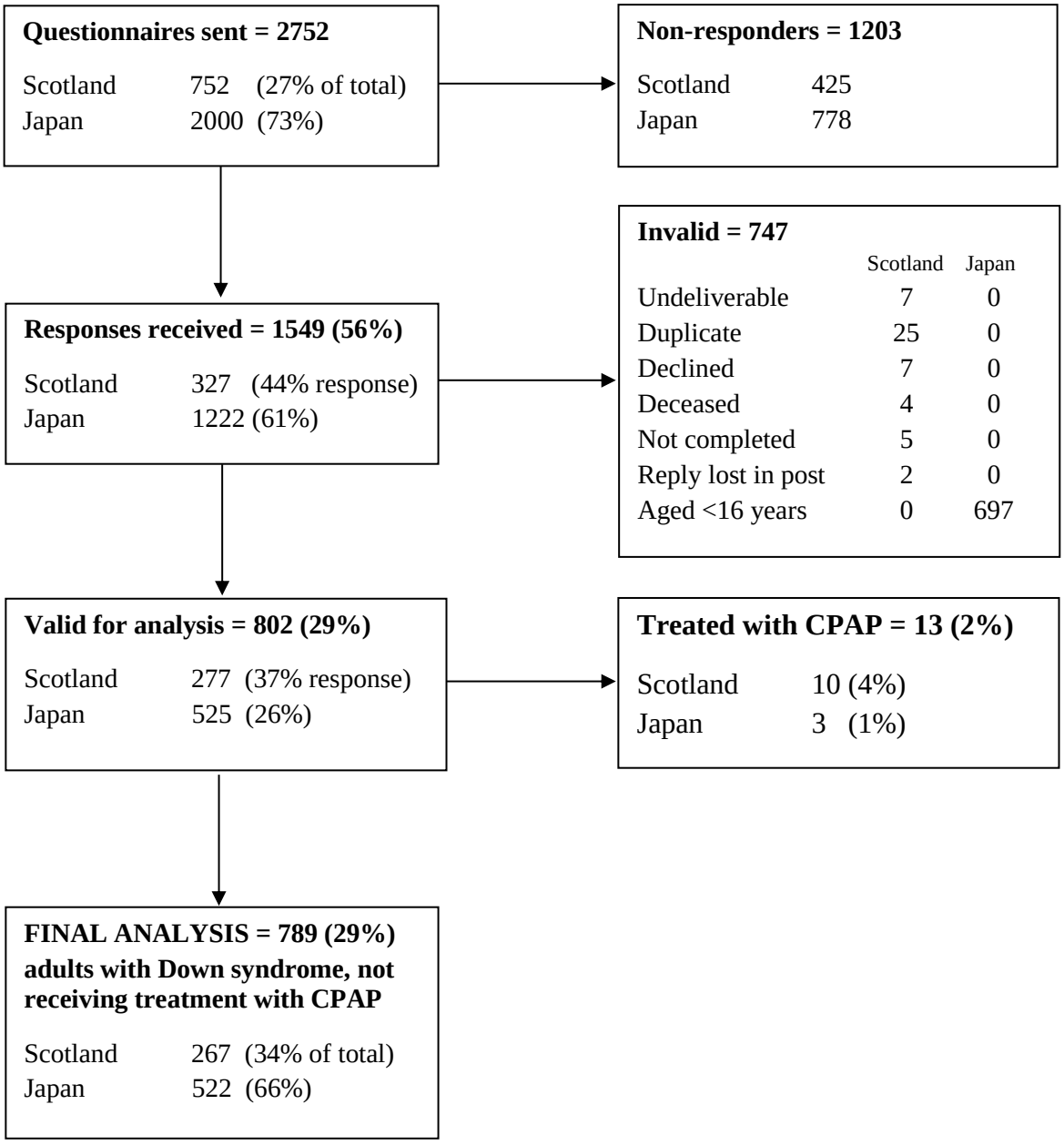
Regression analysis was undertaken to explore significant associations between variables, using binary logistic regression (reported as odds ratio (OR) with 95% confidence interval (CI)) for categorical variables and generalised linear modelling (reported as β-coefficient with 95% CI) for continuous variables. Variables of interest generated by exploration were entered into the appropriate regression model, with the least significant variables then removed from the model in a stepwise fashion. Age, gender and BMI were left in the model to control for the effect of these.

6.2 Results

A summary of the questionnaires sent, responses received and questionnaires valid for analysis is shown in Figure 18. Of a total of 2752 questionnaires sent (752 in Scotland, 2000 in Japan), 789 were valid for analysis – 267 (34%) from participants in Scotland and 522 (66%) from participants in Japan. Thirteen responders had a prior diagnosis of OSAHS and were using CPAP therapy (4% of all responders in Scotland and 1% in Japan); these individuals were excluded from further analysis.

The characteristics of valid responders in Scotland and Japan are summarised in Table 14. Responders were generally young adults, 56% of whom were male. Mean (p)ESS scores were broadly within the normal range (6±5/24). No significant differences were noted between the two populations in terms of gender, (p)ESS or proportion of individuals exhibiting excessive daytime sleepiness (EDS). However, the Scottish cohort were significantly older than the Japanese population, and had a higher mean BMI. Three-quarters of the Scottish group were overweight or obese, in comparison with 43% of the individuals in Japan. Fifty-six percent of the responders in Japan met the WHO criteria for increased or high risk BMI.

Figure 18: Summary of questionnaires sent, received and valid for inclusion in the study from Japan and Scotland.



Symptoms of OSAHS were common in both cohorts. Snoring (Scotland 68%, Japan 79%; p=0.001) and frequent night awakenings (Scotland 50%, Japan 59%; p=0.04) were significantly more prevalent in the Japanese group. Daytime sleepiness *per se* was more frequently reported in the Scottish population (Scotland 54%, Japan 33%; p<0.0001), despite no significant difference in scores on the (p)ESS between the two countries. Witnessed apnoeas were reported by around a third of responders, with no significant differences between the two cohorts noted.

Gender differences between and within the two populations of adults with DS were explored, and are summarised in Table 15. Participants in Scotland were older than in Japan, irrespective of gender (p<0.0001); however, responders in both countries were predominantly young adults. Mean age did not differ significantly between genders in either country. In Scotland, women had a higher BMI than men, and both men and women in Scotland had a significantly higher BMI than their Japanese counterparts, with higher percentages of individuals in the pre-obese/obese category. Japanese men and women did not differ significantly in terms of BMI risk categorisation. Males were significantly sleepier than females in both Japan and Scotland, with similar mean (p)ESS scores noted within genders in both countries. A higher percentage of men exhibited EDS in the Scottish cohort, a difference not observed in Japan. In Japan, a significantly higher proportion of men than women reported witnessed apnoeas and daytime sleepiness; in Scotland, no significant gender differences in reporting of OSAHS symptoms were noted. Snoring and frequent night awakenings were more common in Japanese than Scottish males. Significantly higher rates of self-reported daytime sleepiness were evident in both males and females in Scotland.

OSAHS prevalence in adults with DS was estimated at 20% in Scotland and 14% in Japan (p=0.08; Table 16). No significant gender differences were noted between or within countries (data not shown).

Regression analysis results for Scotland and Japan are shown in Table 17a/b, Table 19a/b and Table 20a/b respectively. In Japan, male gender was a risk factor for likely OSAHS, though this was not evident in the Scottish cohort. Being male was

the predictor of higher scores on the (p)ESS and EDS in Japan; in Scotland, being younger and being male were also predictive. Age and elevated BMI predicted snoring in both Scotland and Japan, but no significant determinants for witnessed apnoeas were found in either population.

Table 14: Anthropometric and sleep characteristics of responders in Scotland and Japan. Results are shown as mean±SD or number (%) as appropriate.

*** WHO BMI categories valid for individuals aged ≥19 years only.**

Characteristics	Total responses	Whole group n = 789	Scotland n = 267	Japan n = 522	p
Gender (Male : Female)	780	434 : 346 (56% : 44%)	149 : 118 (56% : 44%)	285 : 228 (56% : 44%)	1.00
Age (years)	789	27±10	32±11	25±8	<0.0001
BMI (kg/m^2)	730	25.8±5.8	29.8±7.0	24.0±4.0	<0.0001
*Underweight (<18.5kg/m^2) **	*553*	*16 (3%)*	*1 (0.5%)*	*15 (4%)*	*<0.0001*
*Normal weight **		*242 (44%)*	*52 (25%)*	*190 (57%)*	
*Pre-obese **		*177 (32%)*	*63 (31%)*	*111 (34%)*	
*Obese class I **		*76 (14%)*	*47 (23%)*	*29 (9%)*	
*Obese class II **		*29 (5%)*	*26 (13%)*	*3 (1%)*	
*Obese class III **		*16 (3%)*	*16 (8%)*	*0 (0%)*	
*Increasing but acceptable risk (18.5-23.0kg/m^2) **		-	-	*136 (39%)*	-
*Increased risk (23.0-27.5kg/m^2) **		-	-	*125 (35%)*	
*Higher risk (≥27. 5kg/m^2) **		-	-	*74 (21%)*	
Epworth Sleepiness Score (Pictorial or Japanese)	691	6±5	6±5	6±5	0.39
Excessive daytime sleepiness, i.e. (p)ESS >10/24	691	134 (19%)	46 (20%)	88 (19%)	0.76
Snoring					
ever (≥1 night/week)	741	560 (76%)	163 (68%)	397 (79%)	0.001
Frequently (5-7 nights/week)		154 (21%)	*57 (24%)*	*97 (19%)*	*<0.0001*
Sometimes (1-4 nights/week)		406 (55%)	*106 (44%)*	*300 (60%)*	
Never (<1 night/week)		181 (24%)	*77 (32%)*	*104 (21%)*	
Witnessed apnoeas					
ever (≥1 night/week)	565	183 (33%)	57 (35%)	126 (31%)	0.49
Frequently (5-7 nights/week)		*48 (9%)*	*22 (13%)*	*26 (7%)*	*0.03*
Sometimes (1-4 nights/week)		*135 (24%)*	*35 (21%)*	*100 (25%)*	
Never (<1 night/week)		*382 (68%)*	*107 (65%)*	*275 (69%)*	
Frequent night awakenings					
ever (≥1 night/week)	727	405 (56%)	118 (50%)	287 (59%)	0.04
Frequently (5-7 nights/week)		*81 (11%)*	*35 (15%)*	*46 (9%)*	*0.001*
Sometimes (1-4 nights/week)		*324 (45%)*	*83 (35%)*	*241 (49%)*	
Never (<1 night/week)		*322 (44%)*	*118 (50%)*	*204 (42%)*	
Daytime sleepiness					
ever (≥1 night/week)	771	308 (40%)	136 (54%)	172 (33%)	<0.0001
Frequently (5-7 nights/week)		*49 (6%)*	*38 (15%)*	*11 (2%)*	*<0.0001*
Sometimes (1-4 nights/week)		*259 (34%)*	*98 (39%)*	*161 (31%)*	
Never (<1 night/week)		*463 (60%)*	*117 (46%)*	*349 (67%)*	

Table 15: Gender differences in anthropometric and sleep characteristics of valid questionnaire responders in Scotland and Japan. Results are shown as mean±SD, or number (%) as appropriate.

*** WHO BMI categories valid for individuals aged ≥19 years only.**

Characteristics	Total responses	Scotland n = 267			Japan n = 522			Between groups	
								Male	Female
		Male	Female	p	Male	Female	p	p	p
Age (years)	789	32±11	32±11	0.79	25±8	24±7	0.46	<0.0001	<0.0001
BMI (kg/m^2)	730	28.4±5.5	31.3±8.3	0.006	23.9±4.0	24.1±4.1	0.62	<0.0001	<0.0001
Underweight *	553	*0 (0%)*	*1 (1%)*	*0.002*	*8 (4%)*	*7 (5%)*	*0.62*	*<0.0001*	*<0.0001*
Normal weight *		*34 (30%)*	*18 (20%)*		*111 (58%)*	*76 (50%)*			
Pre-obese *		*39 (34%)*	*24 (26%)*		*55 (29%)*	*53 (35%)*			
Obese class I *		*25 (22%)*	*22 (24%)*		*16 (8%)*	*13 (9%)*			
Obese class II *		*13 (11%)*	*13 (14%)*		*1 (1%)*	*2 (1%)*			
Obese class III *		*3 (3%)*	*13 (14%)*		*0 (0%)*	*0 (0%)*			
Increasing but acceptable risk *		-	-	-	80 (41%)	54 (36%)	0.37	-	-
Increased risk *		-	-	-	67 (35%)	54 (36%)		-	-
Higher risk *		-	-	-	39 (20%)	36 (24%)		-	-
Epworth Sleepiness Score (Pictorial or Japanese)	691	7±6	5±5	0.001	7±5	6±4	0.02	0.71	0.05
Excessive daytime sleepiness, i.e. (p)ESS >10/24	691	33 (25%)	13 (13%)	0.03	54 (22%)	32 (16%)	0.15	0.44	0.61
Snoring≥1 night/week	741	94 (69%)	69 (67%)	0.89	225 (82%)	166 (76%)	0.07	0.002	0.11
Witnessed apnoeas ≥1 night/week	565	31 (34%)	26 (36%)	0.87	77 (36%)	47 (26%)	0.04	0.79	0.17
Frequent night awakenings ≥1 night/week	727	57 (45%)	61 (56%)	0.09	159 (60%)	124 (57%)	0.46	0.005	1.00
Daytime sleepiness ≥1 night/week	771	83 (59%)	53 (47%)	0.08	115 (41%)	55 (24%)	<0.0001	<0.0001	<0.0001

Table 16: Likely OSAHS prevalence in Scotland and Japan. Results are shown as number (%).

Criteria for likely OSAHS	Total responses	Scotland n = 267	Japan n = 522	p
Frequent snoring with witnessed apnoeas ≥1 night/week or (p)ESS>10	717	36 (16%)	59 (12%)	0.24
Frequent snoring with witnessed apnoeas ≥1 night/week or daytime sleepiness ≥1 night/week	726	46 (20%)	66 (13%)	0.04
Likely OSAHS (either)	728	46 (20%)	70 (14%)	0.08

Table 17a: Determinants of sleepiness, witnessed apnoeas and likely OSAHS in adults with DS in Scotland, assessed by binary logistic regression with estimate reported as odds ratio.

Dependent variable	Scotland n=267				
	Total included	Odds Ratio	95% CI lower	95% CI upper	p
Likely OSAHS					
Age	180	0.99	0.95	1.03	0.47
Gender (male)		1	0.47	2.12	0.99
Pre-obese or obese		1.1	0.47	2.57	0.83
Excessive daytime sleepiness, i.e. (p)ESS >10/24					
Age	178	1.03	0.99	1.07	0.17
Gender (male)		3.63	1.46	9.05	0.006
Pre-obese or obese		2.17	0.76	6.19	0.15
Snoring ≥1 night/week					
Age	185	0.96	0.93	0.99	0.01
Gender (male)		1.06	0.55	2.03	0.86
Pre-obese or obese		2.08	1.02	4.25	0.04
Witnessed apnoeas ≥1 night/week					
Age	125	0.96	0.92	1	0.07
Gender (male)		1.15	0.53	2.48	0.72
Pre-obese or obese		1.26	0.53	2.02	0.6

Table 17b: Determinants of sleepiness in adults with DS in Scotland, assessed by generalised linear modelling with estimate reported as β-coefficient.

Dependent variable	Scotland n=267				
	Total included	β- coefficient	95% CI lower	95% CI upper	p
Epworth Sleepiness Score **					
Age	178	0.08	0.01	0.15	0.03
Gender (male)		3.12	1.56	4.57	<0.0001
Pre-obese or obese		2.45	0.78	4.12	0.004

Table 18a: Determinants of snoring, witnessed apnoeas and likely OSAHS in adults with DS in Japan, assessed by binary logistic regression with estimate reported as odds ratio.

Dependent variable	Japan n=525				
	Total included	Odds Ratio	95% CI lower	95% CI upper	p
Likely OSAHS					
Age	317	1	0.96	1.05	0.84
Gender (male)		1.98	1	3.9	0.049
Increased or high risk BMI		1.73	0.89	3.39	0.11
Excessive daytime sleepiness, i.e. (p)ESS >10/24					
Age	301	1.03	1	1.07	0.08
Gender (male)		2.11	1.14	3.91	0.02
Increased or high risk BMI		1.44	0.79	2.63	0.23
Snoring ≥1 night/week					
Age	326	0.95	0.91	0.98	0.004
Gender (male)		1.67	0.95	2.96	0.08
Increased or high risk BMI		1.8	1.02	3.17	0.04
Witnessed apnoeas ≥1 night/week					
Age	259	1	0.97	1.04	0.99
Gender (male)		1.41	0.82	2.41	0.22
Increased or high risk BMI		0.83	0.49	1.41	0.49

Table 18b: Determinants of sleepiness in adults with DS in Japan, assessed by generalised linear modelling, with estimate reported as β-coefficient.

Dependent variable	Japan n=525				
	Total included	β-coefficient	95% CI lower	95% CI upper	p
Epworth Sleepiness Score (Pictorial or Japanese)					
Age	301	0.62	-0.12	0.14	0.1
Gender (male)		1.8	0.77	2.87	0.001
Increased or high risk BMI		0.46	-0.59	1.52	0.39

6.3 Discussion

In this first international, comparative, cross-sectional study of OSAHS symptoms in adults with DS, the overall likely prevalence of OSAHS was 16%. Prevalence of OSAHS was much higher in both countries than is noted in the general population, supporting previous reports of increased risk of OSAHS in adults with DS. However, prevalence did not differ significantly between countries, supporting our hypothesis that ethnicity does not affect the prevalence of OSAHS in adults with DS.

Cephalometric data in Caucasian and Japanese populations have identified a number of craniofacial features which may predispose to OSAHS (Villaneuva et al. 2005), and cephalometric studies have found differences between adolescents with DS and typically-developing controls of the same ethnic background (Suri et al. 2010). Given that the characteristic craniofacial differences observed in individuals with DS are evident regardless of ethnicity, it appears that the DS craniofacial phenotype over-rides underlying ethnicity. Indeed, mouse models of DS exhibit changes to craniofacial dimensions which are directly proportional to those seen in humans, suggesting that the DS phenotype may even transcend species differences (Richtsmeier et al. 2002).

Some gender effects were noted, though these were not uniform between cohorts. Male gender was a significant determinant of likely OSAHS in Japan, but not

Scotland; in Scotland, being male predicted higher (p)ESS scores and EDS. Men were more likely to exhibit EDS than females in both countries. Male gender is a known risk factor for OSAHS in the general population (Young et al. 1993; Malhotra & White 2002), and it would appear that gender exerts an effect in those with DS also. A further gender difference was noted in the Scottish cohort, with women having higher BMI than men, supporting previously published data in adults with DS in Scotland (Melville et al. 2005). This may be related to a number of factors, including underlying thyroid disease and use of oral contraceptives, both of which are associated with weight gain in the general population (Frye 2006; Milionis & Milionis 2013). Hormonal contraception was used by 8% of females in Scotland, but this is not commonplace in women with DS in Japan, reflecting an important cultural difference.

Mean BMI was much lower in Japan than in Scotland regardless of gender. A previous study in the general population (Genta et al. 2008) comparing OSAHS in males of Caucasian and Japanese descent in Brazil found that ethnicity was not associated with severity of OSAHS when Asian-specific obesity cut-offs were used (World Health Organization 2004). Using these thresholds in the current study, raised BMI was a risk factor for higher sleepiness scores in Scotland, but not Japan, which may reflect the effect of differences in the underlying distribution of body fat with ethnicity in the aetiology of OSAHS (Wang et al. 1994). Differences in diet between Japan and Western cultures have been described; the Western diet is high in animal fat and sugar, predisposing to obesity, whilst the Japanese diet is higher in low-fat foods such as rice, soy and fish (Ogce et al. 2008). Environment plays a role, with the diet of Japanese migrants to the US noted to become more "Westernised".

Further, information on living arrangements were not collected during this study. Previous studies have noted variation in BMI with residential status (Prasher 1995), which may contribute to the differences in BMI observed here. Individuals living in residential care are likely to have a more controlled diet that those living at home with family, and so are less likely to be overweight or obese.

Snoring and/or intermittent nocturnal hypoxia due to apnoeas during sleep are known to affect cognitive function, emotion and behaviour in both the general population and in individuals with DS (Engleman & Douglas 2004; Andreou et al. 2002). People with DS are predisposed to early-onset Alzheimer's-type dementia, with neuropathological changes in the brain, such as beta-amyloid plaques and neurofibrillary tangles, evident in nearly all adults with DS by 40 years of age (Wisniewski et al. 1985). It has been proposed that untreated OSAHS may accelerate cognitive decline in adults with DS (Fernandez & Edgin 2013), and so early recognition and treatment of OSAHS may not only improve diurnal behaviour and diminish sleepiness, but may also play a role in slowing cognitive decline and improving overall quality of life.

This study has limitations which come with every self-reported questionnaire study, including responder bias and lack of objective data. Though the response rate was high (56%), selection bias cannot be ruled out. As discussed in Chapter 5, there may be a proxy effect due to caregivers, rather than individuals with DS completing the questionnaire; however, this is more likely to result in conservative estimation of the prevalence of OSAHS.

Increasing age is a known risk factor for OSAHS (Malhotra & White 2002). As life expectancy in individuals with DS continues to rise, with many adults with DS living into their 60s and 70s (Wu & Morris 2013), this may impact on the prevalence of OSAHS in this population. The majority of responders in both cohorts in this study were young adults, and, therefore, the true prevalence of OSAHS in adults with DS may be underestimated. Given that there may be around 47,000 individuals with DS in the UK alone (Wu & Morris 2013), diagnosing and treating OSAHS in this group may impact on economic aspects of healthcare in this group, as well as overall health economic importance.

Future large-scale studies using polygraphy or polysomnography to objectively assess prevalence would be ideal, and this is the focus of Chapter 7 of this thesis. Previous studies using polysomnography in adults with DS have reported an OSAHS prevalence of >80% (Resta et al. 2003; Trois et al. 2009); however, both of these

studies included only small numbers of participants (24 adults across the two studies) and so may not be representative of the DS population as a whole.

6.4 Conclusions

This study is the first to compare self-reported symptoms of OSAHS in two ethnically diverse populations of adults with DS. Although differences were noted with respect to symptoms between countries, the overall prevalence of OSAHS did not differ significantly, and was raised in comparison with that of the general population.

Both gender and ethnic differences may play a role in the expression of OSAHS across different groups of people and cultural differences may affect its reporting. However, many factors predisposing to OSAHS are common to all those with DS, irrespective of where they are born, and the aetiology of OSAHS in DS is complex and multifactorial.

This study highlights that the evaluation and treatment of OSAHS in adults with DS are limited in both countries. Given the elevated prevalence of OSAHS in adults with DS, there is a real need for this to be addressed; in doing so, the potential for improving the health, cognitive function and quality of life of adults with DS of all ethnicities would be much enhanced.

Chapter 7: Objective assessment of prevalence – sleep studies

Following on from the subjective assessment of prevalence via questionnaire, the second phase of the study was designed to assess prevalence of SDB in adults with DS using objective measures.

7.1 Methods

7.1.1 Sleep study invitation

All eligible questionnaire responders who did not check the box to decline further participation were invited to undergo a home sleep study. In order to accurately assess prevalence of SDB/OSAHS by sampling as true a cross-section of the target population as possible, responders were considered eligible if aged ≥16 years with DS and not currently using CPAP; sleep studies were offered regardless of subjective sleepiness, sleep-related symptoms, previous sleep diagnoses or any other variables reported in the questionnaire. However, as discussed in Chapter 5 and on account of the study topic, selection bias was difficult to avoid.

Where the responder had provided contact details on their completed questionnaire, an invitation pack (see Appendix 2), including invitation letter, participant information sheet, carer information sheet, consent form (for information only), reply slip and pre-paid return postage envelope, was sent directly by the study team. All invitation packs were numbered using the participant's individual identification number as per the questionnaire. Questionnaire responders who had indicated willingness to be contacted further but had not provided contact details were sent an invitation pack by the third-party distributor who had sent their original questionnaire, using their individual questionnaire number. Questionnaire responders were asked to complete and return a reply slip, indicating via a simple check-box whether or not they wished to have a home sleep study, or whether they would like to discuss the study with the research team before making a decision. Responders were

not asked to give a reason if indicating that they did not wish to have a sleep study, although, in practice, many responders annotated reasons on the form.

Where a reply slip was not received within 3 months of posting, a reminder was sent. At this point, no further contact was made in the event of no response to the reminder being received.

Initially, only responders in Scotland were invited for sleep studies. Due to the ongoing ethical review around the inclusion of AWI and the number of questionnaire responders from England, Wales and Northern Ireland, it was decided that responders from outwith Scotland would not be contacted until a final decision had been reached. Upon receipt of a favourable ethical opinion allowing inclusion of AWI in March 2013, invitation packs were sent to responders across the whole of the UK, commencing May 2013. These packs included the original invitation letter, updated versions of the participant and carer information sheets, an information sheet for the relative/carer/welfare attorney of AWI, a copy of the informed consent form for AWI (for information only) and a revised reply slip (see Appendix 2). As well as asking whether or not the responder wished to undergo a sleep study, the revised reply slip contained questions regarding the patient's geographical location (Scotland, England, Wales, Northern Ireland) and ability to give consent. The purpose of these questions was to aid the research team in the logistics of scheduling and delivering home sleep studies, since different study-specific procedures applied depending upon the participant's ability to consent and which part of the country in which they resided (see Chapter 4).

With the approval of the ethics committee, all questionnaire responders from Scotland who had previously either declined a sleep study or failed to return a reply slip were sent an updated invitation with a new covering letter, along with the information sheet and consent form for AWI, explaining the change in entry criteria to allow inclusion of AWI (see Appendix 2). Again, this was followed up by a reminder if a reply was not received, with no further contact made to non-responders after this time.

7.1.2 Home sleep study equipment

Home sleep studies were conducted using the Embletta® Gold™ (Embla Systems LLC, Amsterdam, Netherlands) portable sleep diagnostic device – see Figure 19. This is a level III device (Ferber et al. 1994), with capacity to record multiple channels of physiological data. The Embletta® Gold™ and its predecessor, Embletta®, has been used and validated in a number of studies (Dingli et al. 2003; Abdelghani et al. 2007; Smith et al. 2007; Gjevre et al. 2011; Ng et al. 2010).

Figure 19: The Embletta® Gold™ equipment in situ: 1) nasal pressure cannula; 2) thoracic effort band; 3) pulse oximeter; 4) main unit, including body position sensor; 5) abdominal effort band.

As discussed in Chapter 2, current guidelines (SIGN 2003) state that llimited sleep studies to assess respiratory events are an adequate first-line method of diagnostic assessment for OSAHS and that full PSG with EEG-based sleep staging is not required for most patients. It was felt that the less obtrusive nature of a limited study

device, with fewer sensors than a PSG and not requiring an in-patient hospital stay, would be more acceptable to people with DS, many of whom have experienced high levels of medical intervention during their lifetime and may be 'medical-phobic' (Evans et al. 2005). Home sleep studies have been shown to give a similar, and perhaps more representative, quality of sleep in comparison with inpatient hospital sleep studies (Kingshott & Douglas 2000). Limited sleep studies also offer significant cost savings over full PSG (Dingli et al. 2003; J. F. Masa et al. 2011). Channels were recorded in broad accordance with AASM guidelines for full PSG (Iber et al. 2007), as recommended by the AASM guidelines for portable monitoring (Collop et al. 2007), and are discussed in further detail below. The equipment was set up, downloaded and scored using RemLogic-E™ software Version 3.2 (Embla Systems LLC, Amsterdam, Netherlands).

7.1.2.1 Nasal flow

This was recorded using a disposable nasal pressure cannula (Embla Systems, Amsterdam, Netherlands) situated under and inside the nostrils, connected to an internal pressure sensor in the Embletta® Gold™ device. As well as recording nasal airflow, snoring was derived from the pressure sensor. The cannula fits under the nose, loops behind the ears and tightens via a toggle under the chin. Participants were advised to use a small piece of adhesive tape (Mefix®, Mölnlycke Health Care Ltd., Dunstable, UK) over the tubing on each cheekbone to hold the cannula in place during the night. A number of participants in the study reported discomfort from the nasal cannula due to the length of the prongs entering the nostrils. As a result, they and subsequent participants were advised to trim the ends of the prongs to a comfortable length using sharp scissors. This may be related to the midface hypoplasia typical of the DS phenotype (see Chapter 1).

Although the AASM guidelines (Iber et al. 2007) recommend the use of two separate measures of airflow - a nasal pressure cannula and a nasal-oral thermistor – we opted to use only the cannula in this study for the comfort of participants and their ease of use of the equipment. As the nasal pressure cannula provides a more accurate measure of airflow (Budhiraja et al. 2005), we felt that this would be of no detriment to the quality or reliability of the sleep study recording. AASM guidelines also allow

the use of the pressure cannula as an alternative measure in the absence of a scoreable thermistor signal.

7.1.2.2 Respiratory effort

Respiratory effort was recorded via single-use respiratory inductance plethysmography (RIP) effort bands (XactTrace®, Embla Systems LLC, Amsterdam, Netherlands) These provide an indirect, semi-quantitative measure of respiratory effort, measuring the change in electrical signal generated by stretching and relaxation of the copper wire running through the band in response to changing tidal volume. Bands were measured to the individual participant using standardised techniques (Embla Systems LLC 2011), and placed around the thorax at the level of the axilla, and abdomen at the level of the navel. As well as reducing infection risk, single-use belts often provide better signals than reusable belts due to reduced wear and tear and improved patient fit.

7.1.2.3 Pulse oximetry

Pulse oximetry was conducted using a soft, flexible, slip-on oximeter (Nonin Xpod® and Nonin reuseable soft cuff, Nonin Medical N.V., Amsterdam, Netherlands) for participant comfort and ease of application. This is a transmittance oximeter, deriving percentage arterial haemoglobin saturation (%SpO_2) from the amount of red wavelength light transmitted from one side of the finger to the other; that is, the amount of light not absorbed by the haemoglobin. The Embletta® Gold™ transforms the signal from the sensor to provide raw and averaged percentage oxygen saturation (SpO_2), pulse rate and pulse plethysmography waveform (an indicator for peripheral blood flow that can be used to indicate heart rate and to assess the quality of the oximeter signal).

Participants were instructed to close the hand into a fist before taping the oximeter cable to the back of the hand with adhesive tape. This prevents excessive movement of the sensor, which can cause signal artifact, whilst allowing the participant freedom of movement of their hand. Participants were also advised that they could thread the oximeter cable through the arm of their nightwear to minimise pulling of the cable whilst moving around during the night.

7.1.2.4 Body position

The participant's sleeping position was monitored via an internal position sensor built into the Embletta® Gold™ device. This sensor collects gravity information to measure the patient's angle and elevation (whether standing or horizontal), then derives position changes from this data.

7.1.3 Participant education

Participants and their relatives/carers were instructed in the use of the home study equipment during their first visit (Visit 1), either in the Department of Sleep Medicine or at the participant's home, immediately after informed consent was obtained. Usually, education was carried out on an individual basis, but, on occasion, group educations were conducted where two or more patients (usually friends who knew each other and had requested concurrent appointments) attended at the same time. Education sessions lasted a maximum of 30 minutes.

The Embletta® Gold™ was laid out and demonstrated to the participant and their relative/carer by a member of the research team who was fully trained and experienced in the use of the equipment; either a Registered Polysomnographic Technologist (RPSGT) or Registered Nurse (RN). The participant was encouraged to handle and try on the equipment, and familiarise themselves with it in their own time. A full-colour, easy-read instruction sheet was produced, featuring pictorial information including photos of an individual with DS assembling and wearing the Embletta® Gold™. A laminated, A4-sized version of this instruction sheet was used during education and sent home with the participant to use whilst setting up the equipment at home that evening (see Appendix 2). A mobile phone number was provided to allow the family to contact an RPSGT or RN should they experience any problems or questions during set-up of the equipment on the night of the study. Participants were advised to use the equipment for two consecutive nights to allow for the first-night effect (Agnew et al. 1966; Toussaint et al. 1995; Scholle et al. 2003), allowing the patient to acclimatise to the novel situation and maximise the chance of obtaining a good quality study. A morning questionnaire was issued and a liability form was signed by the patient, relative or carer as per normal departmental protocol.

The home study equipment was returned to the department upon completion of the study, either in person or by post. All postage costs were reimbursed to the participant by the investigators.

7.1.4 Scoring studies

All studies were manually validated and scored by one of two experienced RPSGTs (EAH and SW), using standard software. Automatic scoring in conjunction with manual validation has been well-documented as the gold-standard procedure for sleep scoring, as discussed in Chapter 2. Analysis start and stop times were set manually by the RPSGT scoring the study. These were based on the subjective lights on and off times provided in the morning questionnaire, with the scorer using their judgement, based on clinical experience, to approximate sleep onset and offset from observation of the recorded signals.

7.1.4.1 Automatic scoring

Once analysis start/stop times were set, the study was automatically analysed using the inbuilt software algorithm. Default thresholds for automatic scoring were stated in the sleep study report and are detailed here.

7.1.4.1.1 Automatic detection of events

Events were not detected: during movement periods; within the 10 seconds after a movement period; during periods in the upright position.

7.1.4.1.2 Pulse oximetry

An oxygen desaturation event was detected when the oxygen saturation fell by at least 4%. The valid SpO_2 range was from 50% to 100%, except during periods of artifact. All saturation values <50% were considered artifactual and not counted as part of a desaturation event. The valid pulse range was 25-250bpm, except during periods of artifact. An artifact was flagged on the pulse trace when pulse values of <25bpm or >250bpm were found.

7.1.4.1.3 Detection of breathing events

An apnoea was detected when a 10-second portion of the flow signal dropped below 10% of the reference amplitude. A hypopnea was detected when a 10-second portion

of the flow signal dropped below 70% of the reference amplitude and a desaturation event occurred ≤20 seconds after the start of the hypopnea. The reference amplitude was calculated as the mean of the peak amplitudes found in the 100 seconds preceding the event. All events of duration >120.0 seconds were excluded.

7.1.4.1.4 Respiration effort stop detection

Cessation of respiratory effort was marked when intersecting effort stops were found in both the thoracic and abdominal effort belts. A respiration effort stop was detected when the amplitude of a 5-second portion of the signal dropped below 10% of the reference amplitude. The reference amplitude was calculated as the mean of the amplitudes found in a period of 240 seconds preceding the signal drop. All events of duration >120.0 seconds were excluded.

7.1.4.1.5 Snoring detection:

The minimum number of snores needed to create a snoring period was 3. Snoring periods were merged into one if the interval between them was <10 seconds. Snoring periods were allowed to continue through movement periods.

7.1.4.2 Manual validation

Once the automatic analysis was complete, the study was manually validated by the RPSGT, deleting incorrectly-scored events, adding missed events and reclassifying events as required. Manual scoring was based broadly on the current international guidelines for full PSG (Iber et al. 2007). Although recommended (Collop et al. 2007), these guidelines cannot be directly transferred for use with limited studies. The AASM guidelines' definition of a hypopnoea requires the event to be associated with an oxygen desaturation of ≥3% or an arousal; since the Embletta® Gold™, as with all limited cardiorespiratory sleep study equipment, does not incorporate a valid measure of arousal (i.e. EEG), this criterion cannot be accurately confirmed. Therefore, in this study, a hypopnoea was scored if it met the duration and amplitude criteria as set out in the AASM Manual (Iber et al. 2007), but regardless of whether or not there was a ≥3% oxygen desaturation; an event associated with a desaturation clearly meets the criteria, but in the absence of a desaturation, an arousal cannot be ruled out, and so was given the "benefit of the doubt". We opted not to use pulse rate

rises, pulse transit time, peripheral arterial tone or other surrogate markers of arousal due to the paucity of evidence supporting the accuracy of these methods (Masa et al. 2013).

Manual scoring criteria are summarised herein.

7.1.4.2.1 Detection of breathing events

An apnoea was scored when the amplitude of the flow signal was reduced by ≥90%, based on the previous few stable breaths. If at least part of a breathing event met the criteria for an apnoea, the event was scored as such. Apnoeas were classified as obstructive if respiratory effort was maintained or augmented for the duration of the period of reduced flow. Apnoeas associated with a reduction of respiratory effort of ≥90% on both the thoracic and abdominal bands for the duration of the flow reduction were classified as central. An apnoea was scored as mixed when the period of reduced flow was initially associated with a reduction of respiratory effort of ≥90% on both the thoracic and abdominal bands, but effort was resumed prior to the end of the apnoea, i.e. if the apnoea started central then became obstructive.

A hypopnea was scored when the amplitude of the flow signal was reduced by ≥30%, based on the previous few stable breaths, regardless of whether a desaturation was associated with the event or not. Surrogate measures of arousal, e.g. pulse rate rises, were not considered. Hypopnoeas were not further classified as central or obstructive.

Contrary to the automatic scoring criteria, events were scored during the upright position. It is not unusual for patients to sleep sitting upright in a chair or in other unusual upright postures. Indeed, there is some evidence that children with DS and SDB are more likely to sleep in unusual postures (Senthilvel and Krishna 2011), and this may also be the case in adults.

Events were not scored within the 10 seconds after a clear body movement.

7.1.4.2.2 Pulse oximetry

Oxygen desaturations were not manually validated or reviewed.

7.1.4.3 Sleep study reporting

Outcome parameters were generated and reported automatically by the software. Reported outcomes included:

- Total Recording Time (TRT): Duration from analysis start time to analysis stop time.
- Apnoeas/hypopnoeas per hour in bed (AH): Total number of apnoeas and hypopnoeas divided by the TRT in hours.
- Flattening index: A measure of limitation of the airflow signal resulting from partial airway closure which can be an indicator of upper airways resistance, a sub-OSAHS form of sleep-disordered breathing.
- Snoring time presented as a percentage of TRT.
- Mean SpO_2 measured across TRT.
- SpO_2 nadir: Lowest point of oxygen saturation across TRT.
- Oxygen desaturation index (ODI): Total number of ≥4% oxygen desaturation events divided by the TRT in hours.
- Mean heart rate measured across TRT.
- Mean standard deviation of heart rate: Gives a measure of heart rate variability, which can be used as a proxy indicator of autonomic arousals in the absence of an electroencephalographic measure of arousal (Bonnet et al. 2007).
- Body position as a percentage of TRT.

The index time was derived from the total analysed time minus the total of movement time and time in the upright position, i.e.

Index time = TRT - (movement time + upright time).

Once reported by the RPSGT, all studies were reviewed by a consultant physician experienced in sleep medicine (RLR or IM) and suitability for study inclusion confirmed.

Each participant was sent a results letter detailing the outcome of their sleep study in terms of their AH and ODI (Appendix 2), and all suitable participants were invited to proceed to the treatment phase of the study.

7.1.5 Reliability of sleep scoring

A randomly-selected subset of valid studies were scored by both RPSGTs to assess inter-rater variability (10% of studies scored by SW rescored by EAH). Intra-rater reliability was assessed by EAH blindly rescoring a 10% random subset of valid studies previously scored by herself after a period of ≥1 year had elapsed. Scoring concordance is shown in **Error! Reference source not found.**. Bivariate correlation analysis showed good concordance between scorers in terms of overall AH, obstructive apnoeas and hypopnoeas per hour in bed. No significant correlation in central and mixed apnoeas per hour in bed was observed, though this is likely due to the very small number of these events scored (mean <1.0 events per hour in bed by both scorers).

Table 19: Scoring concordance for sleep study variables. Difference presented as median (IQR). Correlation coefficient presented as Spearman's ρ.

Sleep study variables	Scorer 1	Scorer 2	Difference	Spearman ρ	p
Inter-rater reliability (n=6; 10% of total scored by SW)					
Apnoeas/Hypopnoeas per hour in bed	18.8 (12.9-28.6)	24.8 (15.0-31.6)	3.7 (-0.06-5.3)	0.943	0.01
Obstructive	9.6 (4.8-16.2)	7.3 (3.9-12.4)	-2.7 (-4.1--0.2)	0.943	0.01
Central	0.2 (0.1-0.4)	0.3 (0.0-0.4)	0.1 (-0.2-0.1)	0.470	0.35
Mixed	0.1 (0.0-0.6)	0.1 (0.0-0.2)	-0.1 (-0.4-0.1)	0.548	0.26
Hypopnoea	9.5 (5.4-15.6)	17.5 (9.9-19.7)	4.8 (3.4-7.3)	0.943	0.01
Intra-rater reliability (n=7; 10% of total scored by EAH)					
Apnoeas/Hypopnoeas per hour in bed	18.0 (12.1-28.6)	19.9 (13.6-30.0)	1.5 (-3.6-1.9)	0.964	<0.0001
Obstructive	3.8 (2.4-9.0)	5.9 (4.5-7.3)	1.1 (-0.9-2.1)	0.786	0.04
Central	0.1 (0.0-0.6)	0.2 (0.1-0.6)	0.0 (-0.1-0.2)	0.692	0.09
Mixed	0.0 (0.0-0.6)	0.0 (0.0-0.1)	0.0 (0.0-0.0)	0.197	0.67
Hypopnoea	15.1 (6.8-24.6)	14.9 (9.5-20.4)	-0.2 (-4.6-1.0)	0.964	<0.0001

7.2 Results

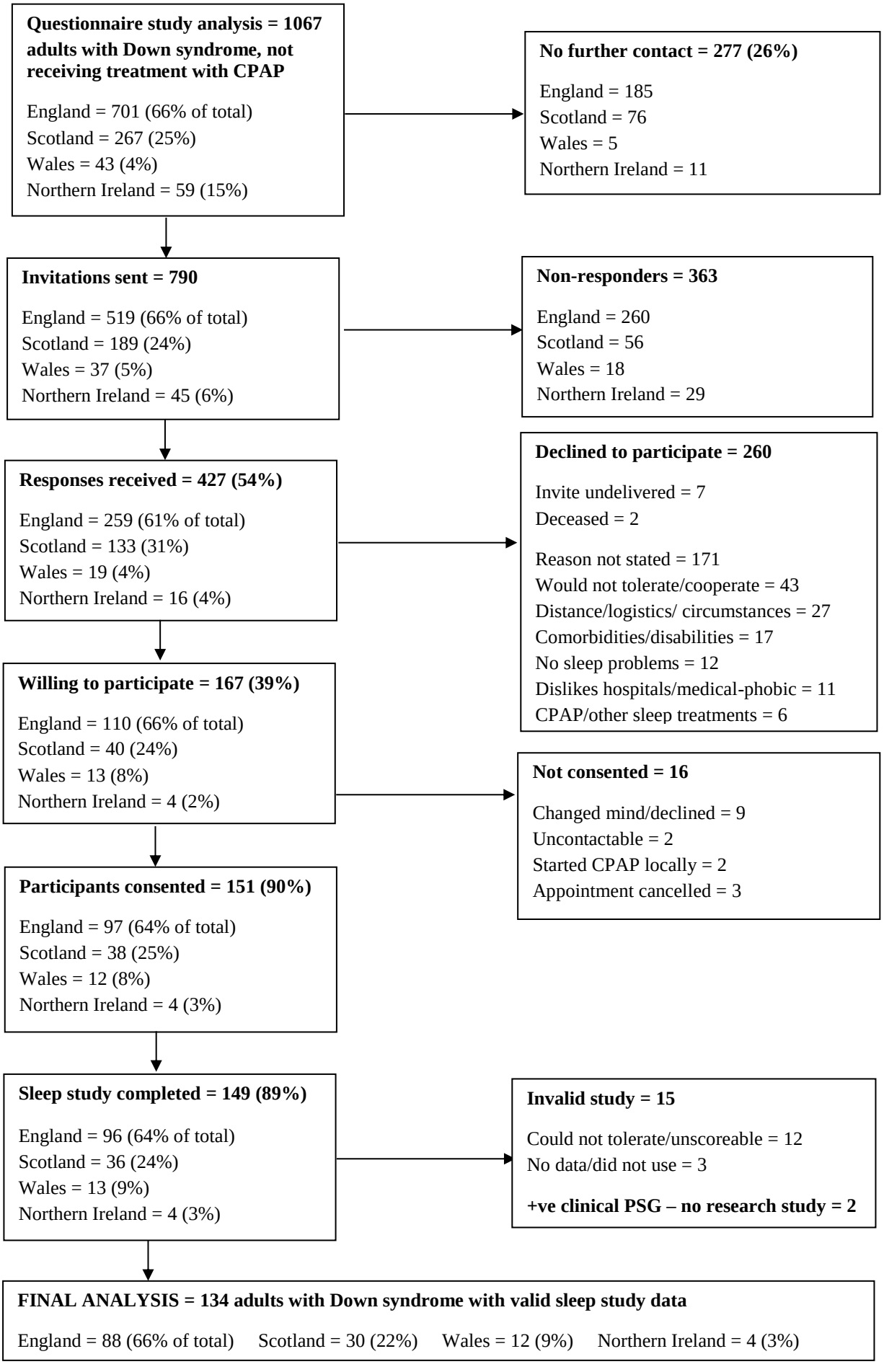
Study participation is summarised in Figure 20. Of the 1067 valid questionnaire responders not currently receiving CPAP therapy, 277 (26%) did not wish to be contacted further. Of the 790 invitations sent, 427 responses were received (54%), 260 of which declined to participate. Although a reason for declining was not sought, a number of responders annotated their reply slip with a reason; common reasons for declining participation included belief that the individual with DS would not tolerate the equipment or cope with the study (17%), the logistics of the study or general family circumstances making participation problematic (10%), other existing comorbidities or disabilities (7%) and a general dislike of hospitals/medical intervention (4%). Twelve individuals (5%) declined to participate because they did not perceive themselves to have a sleep problem. Six individuals reported that they were on CPAP or other sleep treatments and so were ineligible for further inclusion.

One hundred and sixty seven individuals were willing to undergo a home sleep study. Of these, 151 (90%) completed informed consent and were formally recruited into the study. Of those who were not consented, 9 changed their mind and declined to participate, 2 could not be contacted to book an appointment and a further 2 had commenced CPAP through a local clinical service since returning a reply slip. Three individuals cancelled appointments and were not rebooked.

One hundred and forty nine individuals underwent home sleep studies; two of the consented individuals were recruited on the basis of clinical polysomnography studies in the Department of Sleep Medicine, RIE, and did not undergo a home sleep study. Of the recorded studies, 15 studies (10%) did not yield valid results, with 12 studies being unscoreable or not tolerated, and 3 studies having no data recorded or not been used, and were not repeated. Therefore, the final analysis is based on 134 adults with DS with valid home sleep study data.

The majority of participants (66%) lived in England, with 22% in Scotland, 9% in Wales and 3% in Northern Ireland.

Figure 20: CONSORT diagram detailing participants included and excluded from objective sleep study.



7.2.1 Anthropometric data

The subset of participants in the sleep study appears to be broadly representative of the questionnaire study cohort as a whole. Anthropometric characteristics of all sleep study participants, taken from their completed prevalence questionnaire, are summarised in Table 20. Participants were mainly young adults (mean age 26±8 years). The mean BMI was 30.3±6.4kg/m^2, with females significantly heavier than males (28.6±6.1 v. 32.5±6.2; p=0.001). Of the 90 individuals aged ≥20 years for whom the WHO international classification of BMI are valid (World Health Organization 2006), 76% were overweight or obese – see Figure 21.

7.2.2 Comorbidities and medication

Comorbidities and medication use were generally in line with the results of the questionnaire study (see Chapter 5), with 74% of participants using at least one medication, as shown in Table 20. As one would expect in this population, thyroid (38%) and heart disorders (39%) were prevalent. Respiratory problems were also noted, with 24% reporting hay fever and 15% asthma. This was reflected in the use of medications, with 41% using category H drugs (systemic hormonal preparations, which includes thyroxine) and 17% using category R (respiratory system) medications. Use of medications affecting sleep, including benzodiazepines, antidepressants, opiates, oxygen, melatonin and antihistamines were low, ranging between <1% and 8% (1-10 individuals). No significant gender differences in comorbidities and medication were noted, other than in use of category G medications (genito-urinary system and sex hormones), which were used more frequently by females (p<0.0001) due to the inclusion of contraceptives in this category (20% of female participants). Twenty-five percent of participants had previously undergone tonsil and/or adenoid surgery.

Figure 21: BMI classification of participants aged ≥20 years using the World Health Organisation International Classification (World Health Organization 2006). n=90 (53 males), p=0.003.

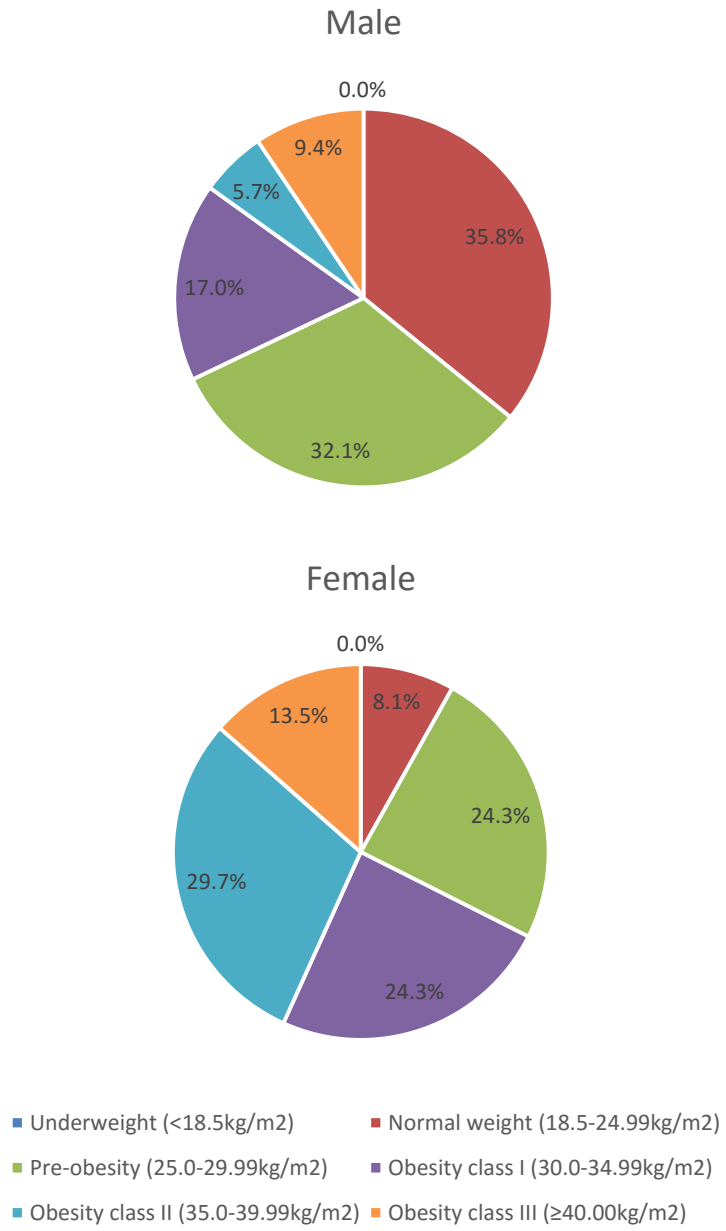


Table 20: Anthropometric characteristics of all sleep study participants. Chi-square test used for parametric categorical variables and t-test for continuous categorical variables. Values presented as mean±SD or n%.

*** Difference between males and females**

**** 2 males did not complete a questionnaire**

***** WHO BMI category calculated for participants aged ≥20 years only**

****** Includes oxygen**

Characteristics	Total included	All participants n = 134		Male n = 78 (58%) **		Female n = 56 (42%)		p *
Age (years)	133	26 ± 8		25 ± 7		26 ± 9		0.68
Body Mass Index (kg/m^2) ***	114	30.3 ± 6.4		28.6 ± 6.1		32.5 ± 6.2		0.001
Underweight (<18.5kg/m^2)	90	0	0.0%	0	0.0%	0	0.0%	0.003
Normal weight (18.5-24.99kg/m^2)		22	24.4%	19	35.8%	3	8.1%	
Pre-obesity (25.0-29.99kg/m^2)		26	28.9%	17	32.1%	9	24.3%	
Obesity class I (30.0-34.99kg/m^2)		18	20.0%	9	17.0%	9	24.3%	
Obesity class II (35.0-39.99kg/m^2)		14	15.6%	3	5.7%	11	29.7%	
Obesity class III (≥40.00kg/m^2)		10	11.1%	5	9.4%	5	13.5%	
Collar size (cm)	86	40.7 ± 4.2		41.5 ± 3.3		39.1 ± 5.2		0.03
Comorbidities:								
Asthma	132	20	15.2%	16	21.1%	4	7.1%	0.03
Stroke	132	2	1.5%	0	0.0%	2	3.6%	0.18
Broken nose	132	1	0.8%	0	0.0%	1	1.8%	0.42
Diabetes	132	4	3.0%	2	2.6%	2	3.6%	1.00
Heart problems	132	51	38.6%	24	31.6%	27	48.2%	0.07
Hay fever	132	31	23.5%	18	23.7%	13	23.2%	1.00
Thyroid problems	132	50	37.9%	25	32.9%	25	44.6%	0.21
Epilepsy	132	3	2.3%	3	3.9%	0	0.0%	0.26
Liver problems	132	1	0.8%	1	1.3%	0	0.0%	1.00
Hypertension	132	1	0.8%	0	0.0%	1	1.8%	0.42
Nasal surgery	132	2	1.5%	1	1.3%	1	1.8%	1.00
Kidney problems	132	1	0.8%	1	1.3%	0	0.0%	1.00
Gluten intolerance	132	9	6.8%	3	3.9%	6	10.7%	0.17
Any adenoid and/or tonsil surgery	132	33	25.0%	18	23.7%	15	26.8%	0.69
Any medication	132	97	73.5%	51	67.1%	46	82.1%	0.07
A - Alimentary tract and metabolism	132	34	25.8%	18	23.7%	16	28.6%	0.55
B - Blood and blood forming organs	132	3	2.3%	1	1.3%	2	3.6%	0.57
C - Cardiovascular system	132	9	6.8%	3	3.9%	6	10.7%	0.17
D - Dermatologicals	132	15	11.4%	8	10.5%	7	12.5%	0.79
G - Genito-urinary system and sex hormones	132	15	11.4%	1	1.3%	14	25.0%	<0.0001
H - Systemic hormonal preparations, excluding sex hormones and insulins	132	54	40.9%	28	36.8%	28	50.0%	0.29
J - Antiinfectives for systemic use	132	2	1.5%	1	1.3%	1	1.8%	1.00
L - Antineoplastic and immunomodulating agents	132	0	0.0%	0	0.0%	0	0.0%	-
M - Musculo-skeletal system	132	8	6.1%	4	5.3%	4	7.1%	0.72
N - Nervous system	132	17	12.9%	10	13.2%	7	12.5%	1.00
P - Antiparasitic products, insecticides and repellents	132	0	0.0%	0	0.0%	0	0.0%	-
R - Respiratory system	132	23	17.4%	15	19.7%	8	14.3%	0.49
S - Sensory organs	132	2	1.5%	1	1.3%	1	1.8%	1.00
V - Various ****	132	1	0.8%	0	0.0%	1	1.8%	0.42
Over-the-counter medications with no clear WHO ATC category	132	9	6.8%	3	3.9%	6	10.7%	0.17
Benzodiazepines	132	1	0.8%	1	1.3%	0	0.0%	1.00
Antidepressants	132	4	3.0%	1	1.3%	3	5.4%	0.31
Opiates	132	2	1.5%	0	0.0%	2	3.6%	0.18
Oxygen	132	1	0.8%	0	0.0%	1	1.8%	0.42
Melatonin	132	1	0.8%	1	1.3%	0	0.0%	1.00
Antiepileptics	132	4	3.0%	2	2.6%	2	3.6%	1.00
Contraceptives	132	11	8.3%	-	-	11	19.6%	-
Antihistamines	132	10	7.6%	5	6.6%	5	8.9%	0.74

7.2.3 Sleep symptoms

Sleep and behaviour characteristics are summarised in Table 21, and appear to be a representative subset of the population surveyed. The mean pESS was 9±6, with 32% reporting a pESS of >10, indicative of EDS (in comparison to a mean pESS of 7±5 in the subjective prevalence cohort, 23% of whom reported EDS). However, daytime sleepiness was reported at least once per week by 85% of responders. Eighty-three percent of responders reported snoring at least 1 night per week, 59% frequently, with witnessed apnoeas ≥1 night/week reported by 40%, 20% frequently, although 45% did not know whether they had breathing pauses during sleep or not. Nocturnal choking episodes ≥1 night/week were noted by 35%. Frequent night wakenings (81%) and unrefreshing sleep (85%) on ≥1 night/week were also prevalent.

The mean estimated TST in 24hr was 9.0±1.4hr, with a trend towards females sleeping longer than males (p=0.002) observed, similar to the questionnaire cohort. There was no significant gender difference in estimated TST during the night (8.4±1.2; p=0.14) or during the day (0.0 (0.0-1.0); p=0.13). Thirty-eight percent of participants reported daytime napping, with a trend towards more napping in females (29% v. 49%; p=0.07).

Using the same algorithms as the questionnaire study (Fuhrman et al. 2012), 56% of sleep study participants met the criteria for probable OSAHS on at least one of the 3 algorithms, in contrast to 35% of the questionnaire study participants. Eight percent (10 participants) had an existing diagnosis of OSAHS.

7.2.4 Behavioural and emotional disturbances

Behaviour scores on the 3 subscales of the DBC-A (Table 21) were similar to those obtained overall in the questionnaire study, although the significant gender differences observed in the Disruptive behaviour subscale in the questionnaire study were not apparent in this subset. No significant gender differences were noted in terms of total scores, mean items scores or the breadth or intensity of problem behaviours.

Table 21: Self-reported sleep and behaviour characteristics of sleep study participants. Chi-square test used for parametric categorical variables, t-test for continuous categorical variables and Mann-Whitney U test for non-parametric variables. Values presented as mean±SD, median(IQR) or n % unless otherwise stated.

*** Difference between males and females**

**** 2 males did not complete a questionnaire**

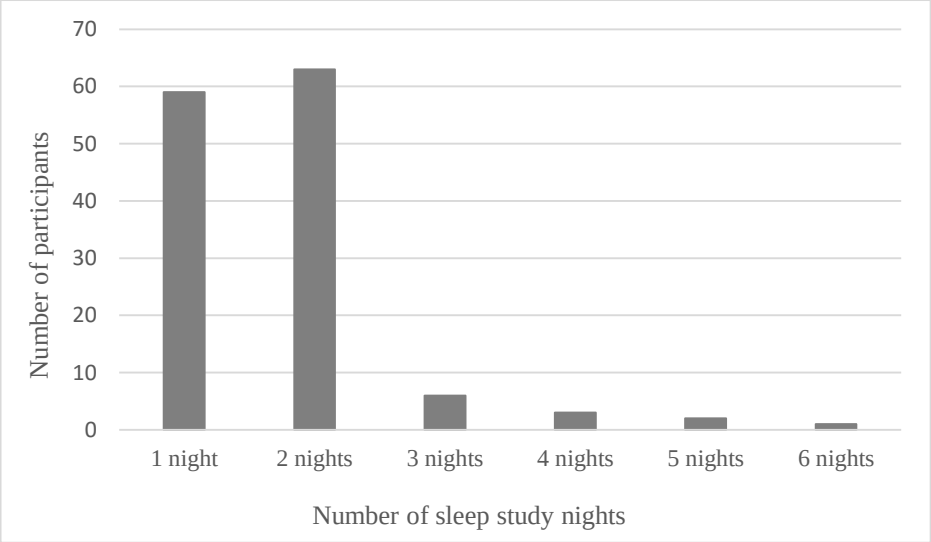
Sleep and behaviour characteristics	**Total included**	**All participants n = 134**		**Male n = 78 (58%) ****		**Female n = 56 (42%)**		**p ***
Developmental Behaviour Checklist for Adults (DBC-A):								
Disruptive behaviour subscale (scale range 0-34)	129	6 (2-10)		6 (2-10)		6 (3-10)		0.93
Mean item score (possible score 0-2)	129	0.35 (0.12-0.62)		0.35 (0.12-0.65)		0.35 (0.16-0.60)		0.95
Proportion of items checked (possible score 0-1)	129	0.29 (0.12-0.53)		0.29 (0.12-0.47)		0.29 (0.16-0.59)		0.84
Intensity index (possible score 0-1)	119	0.00 (0.00-0.33)		0.00 (0.00-0.33)		0.00 (0.00-0.29)		0.62
Anxiety/Antisocial subscale (scale range -2-14)	129	0 (0-1)		0 (0-2)		0 (0-1)		0.29
Mean item score (possible score 0-2)	129	0.22 (0.00-0.44)		0.22 (0.11-0.44)		0.11 (0.00-0.36)		0.28
Proportion of items checked (possible score 0-1)	129	0.11 (0.00-0.33)		0.22 (0.11-0.33)		0.11 (0.00-0.33)		0.26
Intensity index (possible score 0-1)	96	0.00 (0.00-0.50)		0.00 (0.00-0.50)		0.00 (0.00-0.50)		0.87
Depressive subscale (scale range 0-18)	129	2 (0-5)		2 (0-5)		3 (1-5)		0.18
Mean item score (possible score 0-2)	129	0.22 (0.00-0.55)		0.22 (0.00-0.56)		0.33 (0.08-0.58)		0.17
Proportion of items checked (possible score 0-1)	129	0.22 (0.00-0.44)		0.11 (0.00-0.44)		0.23 (0.08-0.56)		0.13
Intensity index (possible score 0-1)	95	0.00 (0.00-0.25)		0.00 (0.00-0.25)		0.00 (0.00-0.33)		0.99
Pictorial Epworth Sleepiness Scale (pESS)	118	9 ± 6		9 ± 6		9 ± 5		0.72
Pictorial Epworth Sleepiness Scale score >10	118	38	32.2%	22	32.8%	16	31.4%	1.00
Estimated total sleep time (TST) in 24 hours (hr)	68	9.0 ± 1.4		8.6 ± 1.3		9.6 ± 1.3		0.002
Estimated TST during night (hr)	124	8.4 ± 1.2		8.3 ± 1.2		8.6 ± 1.2		0.14
Estimated TST during daytime (hr)	103	0.0 (0.0-1.0)		0.0 (0.0-1.0)		0.0 (0.0-1.0)		0.13
Naps in daytime	103	39	37.9%	17	29.3%	22	48.9%	0.07
Snoring - *ever (≥1 night/week)*	129	*107*	*82.9%*	*63*	*86.3%*	*44*	*78.6%*	-
Never		15	11.6%	7	9.6%	8	14.3%	0.19
Rarely/sometimes (1-2 night/week)		31	24.0%	16	21.9%	15	26.8%	
Often/frequent (≥3 nights/week)		76	58.9%	47	64.4%	29	51.8%	
Don't know		7	5.4%	3	4.1%	4	7.1%	-
Witnessed apnoeas - *ever (≥1 night/week)*	130	*52*	*40.0%*	*30*	*40.0%*	*22*	*40.0%*	-
Never		19	14.6%	15	20.0%	4	7.3%	0.16
Rarely/sometimes (1-2 night/week)		22	16.9%	11	14.7%	11	20.0%	
Often/frequent (≥3 nights/week)		30	23.1%	19	25.3%	11	20.0%	
Don't know		*59*	*45.4%*	*30*	*40.0%*	*29*	*52.7%*	-

Nocturnal choking episodes - *ever (≥1 night/week)*		*45*	*34.6%*	*25*	*33.3%*	*20*	*36.4%*	-
Never		63	48.5%	35	46.7%	28	50.9%	
Rarely/sometimes (1-2 night/week)	130	37	28.5%	19	25.3%	18	32.7%	0.48
Often/frequent (≥3 nights/week)		8	6.2%	6	8.0%	2	3.6%	
Don't know		*22*	*16.9%*	*15*	*20.0%*	*7*	*12.7%*	-
Frequent night wakenings - *ever (≥1 night/week)*		*106*	*80.9%*	*56*	*73.7%*	*50*	*90.9%*	-
Never		14	10.7%	12	15.8%	2	3.6%	
Rarely/sometimes (1-2 night/week)	131	69	52.7%	35	46.1%	34	61.8%	0.06
Often/frequent (≥3 nights/week)		37	28.2%	21	27.6%	16	29.1%	
Don't know		*11*	*8.4%*	*8*	*10.5%*	*3*	*5.5%*	-
Unrefreshing sleep - *ever (≥1 night/week)*		*110*	*84.0%*	*60*	*80.0%*	*50*	*89.3%*	-
Never		12	9.2%	10	13.3%	2	3.6%	
Rarely/sometimes (1-2 night/week)	131	52	39.7%	24	32.0%	28	50.0%	0.77
Often/frequent (≥3 nights/week)		58	44.3%	36	48.0%	22	39.3%	
Don't know		*9*	*6.9%*	*5*	*6.7%*	*4*	*7.1%*	-
Daytime sleepiness - *ever (≥1 night/week)*		*111*	*84.7%*	*63*	*84.0%*	*48*	*85.7%*	-
Never		19	14.5%	11	14.7%	8	14.3%	
Rarely/sometimes (1-2 night/week)	131	59	45.0%	35	46.7%	24	42.9%	0.84
Often/frequent (≥3 nights/week)		52	39.7%	28	37.3%	24	42.9%	
Don't know		*1*	*0.8%*	*1*	*1.3%*	*0*	*0.0%*	-
Obstructive sleep apnoea (OSA) status:								
Prior diagnosis of OSA	132	10	7.6%	7	9.2%	3	5.4%	0.52
Probable OSA using definition 1	129	70	54.3%	42	57.5%	28	50.0%	0.48
Probable OSA using definition 2	129	72	55.8%	44	60.3%	28	50.0%	0.29
Probable OSA using definition 3	129	70	54.3%	42	57.5%	28	50.0%	0.48
Probable OSA on ≥1 definition	129	72	55.8%	44	60.3%	28	50.0%	0.29

7.2.5 Objective sleep data

The home sleep study equipment was generally well-accepted, with scoreable results achieved on night 1 or 2 of the study in the majority of cases (Figure 22: Number of home sleep study nights required to obtain a valid diagnostic outcome.). Twelve individuals (9%) required a repeat study to obtain a scoreable result. The nasal airflow signal was not sufficient to provide a valid AH per hour in bed in 14 participants, and so the ODI was used for diagnosis. Nineteen did not have a valid oximetry signal but had a valid AH.

Figure 22: Number of home sleep study nights required to obtain a valid diagnostic outcome.



Objective sleep study data are shown in Table 22. The total scored recording time averaged 488.4±115.1min (8.1±2.6hr), similar to the estimated TST at night reported subjectively via questionnaire (8.4±1.2hr), and did not differ significantly between genders.

Table 22: Manually-scored objective sleep study characteristics of male and female participants. Chi-square test used for parametric categorical variables, t-test for continuous categorical variables and Mann-Whitney U test for non-parametric variables. Values presented as mean±SD, median(IQR) or n % unless otherwise stated.

*** Difference between males and females**

**** 2 males did not complete a questionnaire**

Sleep study variables	Total included	All participants n = 134		Male n = 78 (58%) **		Female n = 56 (42%)		p *
Total recording time (min)	132	488.4 ± 115.1		485.4 ± 123.3		492.6 ± 103.5		0.72
Apnoeas/Hypopnoeas per hour in bed	120	21.8 (10.9-42.7)		25.4 (12.8-45.1)		15.2 (7.1-30.7)		0.01
Supine	120	24.7 (10.0-46.9)		28.7 (15.1-52.6)		20.0 (2.2-39.0)		0.03
Non-supine	120	8.8 (3.0-22.1)		7.8 (2.4-23.1)		8.9 (3.0-21.8)		0.91
Obstructive	118	4.6 (1.2-16.9)		8.0 (1.6-18.3)		3.2 (0.6-15.4)		0.06
Central	118	0.2 (0.0-0.8)		0.45 (0.0-1.2)		0.0 (0.0-0.3)		0.002
Mixed	118	0.0 (0.0-0.4)		0.0 (0.0-0.5)		0.0 (0.0-0.2)		0.12
Hypopnoea	119	13 (6.7-20.9)		14.8 (7.4-23.6)		6.9 (5.7-16.8)		0.01
Flattening index	95	10.1 (5.0-17.9)		9.1 (4.5-15.0)		12.1 (6.9-24.9)		0.17
Mean SpO2 (%)	115	94 ± 3		94 ± 3		93 ± 4		0.73
SpO2 nadir (%)	114	81 ± 8		81 ± 8		81 ± 9		0.70
Average desaturation (%)	115	5 ± 1		5 ± 1		5 ± 1		0.80
Oxygen desaturation index per hour in bed	114	6.6 (2.3-20.0)		8.9 (3.6-21.7)		3.0 (1.6-13.2)		0.01
Supine	114	7.6 (1.6-24.1)		10.2 (3.1-25.9)		2.8 (0.9-11.4)		0.02
Non-supine	114	2.2 (0.5-8.0)		2.6 (0.3-8.0)		1.7 (0.5-9.4)		0.80
Mean heart rate (BPM)	115	63.4 ± 10.6		61.4 ± 11.1		66.1 ± 9.3		0.02
Mean standard devation of heart rate (BPM)	115	6.6 ± 3.1		7.0 ± 3.6		5.9 ± 2.1		0.07
Body position:								
Supine % of total recording time	132	47.8 ± 33.7		57.2 ± 33.5		35.1 ± 29.8		<0.0001
Left % of total recording time	132	8.6 (0.0-32.5)		8.8 (0.0-31.5)		6.7 (0.0-36.3)		0.31
Prone % of total recording time	132	1.8 (0.0-18.1)		0.3 (0.0-13.1)		9.6 (0.0-32.0)		0.002
Right % of total recording time	132	11.2 (0.0-29.2)		4.7 (0.0-28.4)		18.1 (0.1-34.4)		0.01
Upright % of total recording time	132	0.1 (0.0-0.8)		0.0 (0.0-0.8)		0.1 (0.0-0.8)		0.38
Transition index per hour in bed	132	2.0 (0.9-3.5)		1.6 (0.7-3.3)		2.5 (1.5-3.8)		0.02
Sleep-disordered breathing (SDB):								
AH ≥ 10	120	93	77.5%	58	84.1%	35	68.6%	0.05
AH ≥ 15	119	74	62.2%	48	69.6%	26	52.0%	0.58
ODI ≥ 10	114	47	41.2%	31	47.0%	16	33.3%	0.18
Obstructive sleep apnoea/hypopnoea syndrome (OSAHS):								
AH ≥ 15 + pESS >10	120	24	20.0%	16	22.9%	8	16.0%	0.49
AH ≥ 15 + unrefreshing sleep often/frequently	118	35	29.7%	25	36.2%	10	20.4%	0.70
AH ≥ 15 + daytime sleepiness often/frequently	128	30	23.4%	20	26.7%	10	18.9%	0.40
OSAHS on >1 definition	118	49	41.5%	34	48.6%	15	31.3%	0.09

7.2.5.1 Breathing events

The mean AH per hour in bed was 21.8(10.9-42.7), with a trend towards a higher AH noted in males (p=0.01). As would be expected, the supine AH (24.7(10.0-46.9)) was higher than the non-supine value (8.8(3.0-22.1)). The majority of scored events were hypopnoeas, and the majority of scored apnoeas were obstructive, rather than central or mixed. The flattening index, which can be an indicator of flow limitation, was 10.1 (5.0-17.9) per hour.

7.2.5.2 Pulse oximetry

The mean ODI per hour was 6.6 (2.3-20.0), trending towards a higher ODI in males (p=0.01). Again, values were higher in the supine (7.6(1.6-24.1)) versus non-supine (2.2(0.5-8.0)) position. The mean baseline saturation was 94±3%, which is within normal limits, with an SpO2 nadir of 81±8% and mean desaturation of 5±1%. Despite the raised BMI of participants, obesity hypoventilation was not observed in any individual.

7.2.5.3 Heart rate variability

The mean heart rate was 63.4±10.6 BPM, within the normal range for adults. The mean standard deviation of the heart rate, was 6.6±3.1 BPM; this indicates a degree of heart rate variability, a proxy measure for autonomic arousal (Bonnet et al. 2007), suggesting a degree of sleep fragmentation.

7.2.5.4 Body position

The highest percentage of recording time was noted in the supine position. Males, on average, spent over half of the study supine (57.2±33.5%), with females supine for significantly less time (35.1±29.8%; p<0.0001). Females tended to spend more time prone than males, although this did not reach significance (p=0.002). Very little time was spent in the upright position (0.1(0.0-0.8)%). The transition index, which gives an indication of position changes and, therefore, restlessness, was low (2.0(0.9-3.5) per hour).

7.2.6 Diagnosis of OSAHS

In terms of diagnostic thresholds, 78% met the AH criteria for entry to the treatment study, with an AH≥10. An AH≥15 or an ODI ≥10/hr is considered diagnostic of OSA using the SIGN guidelines (Scottish Intercollegiate Guidelines Network 2003); 62% met the SIGN criteria for AH and 41% the criteria for ODI.

The probable OSAHS algorithms (Fuhrman et al. 2012) were adapted, in line with the SIGN guidelines, to allow direct comparison of the subjective diagnosis of probable OSAHS with the objective diagnosis of OSAHS by substituting snoring ≥3 nights/week and witnessed apnoeas with AH≥15:

4. AH≥15 plus pESS>10.
5. AH≥15 plus unrefreshing sleep ≥3 nights per week.
6. AH≥15 plus daytime sleepiness ≥3 nights per week.

Using these modified algorithms, 42% of participants demonstrated OSAHS on ≥1 definition (versus 56% of the same group who met the criteria for probable OSAHS).

Subjective and objective measures of OSAHS were compared – see Table 23. Sensitivity of the probable OSAHS algorithms (ability of the algorithms to correctly identify individuals with objectively-diagnosed OSAHS) was 79.2%, with a specificity (ability of the algorithms to correctly identify individuals who do not have OSAHS) of 58.5%. The positive predictive value (PPV; the likelihood of an individual to have OSAHS in the event of meeting the criteria for probable OSAHS via the algorithms) was 58.5% and the negative predictive value (NPV; the likelihood of an individual to be OSAHS negative in the event of obtaining a negative result on the algorithms) was 79.2%. The likelihood ratio (how much more likely it is that an individual who is positive for probable OSAHS via the algorithms will have an objective diagnosis of OSAHS) was 1.9 (Lalkhen & McCluskey 2008).

Characteristics of individuals with and without OSAHS are summarised in Table 24. No significant gender differences were noted in terms of age, gender, BMI, collar size or comorbidities or medications related to sleep between those with and without a diagnosis of OSAHS; those with a diagnosis of OSAHS via home sleep study were

more likely to have thyroid problems, though this did not reach statistical significance (p=0.01).

Sleep and behaviour characteristics of those with and without a diagnosis of OSAHS are shown in Table 25. Self-reported symptoms including snoring, nocturnal choking episodes, unrefreshing sleep and daytime sleepiness were significantly higher in the OSAHS positive group (all p<0.0001, except nocturnal choking episodes p=0.001). Witnessed apnoeas did not differ significantly between those with and without OSAHS, although the number of individuals who did not know whether or not they had apnoeas was high in both groups (45% of OSAHS group and 46% of those without OSAHS). Ninety-four percent of those with OSAHS reported snoring, although 79% of those without OSAHS were also snorers.

The mean pESS was significantly higher in those with OSAHS (11±6 v 7±5; p=0.001), with 55% of the OSAHS positive group exhibiting EDS on the pESS, versus 18% of those without OSAHS (p<0.0001), although 71% of those with OSAHS and 24% of the OSAHS negative group reported daytime sleepiness ≥3 nights per week. Seventy-nine percent of the OSAHS group were correctly identified using the probable OSAHS algorithms, while 42% of those not exhibiting OSAHS via objective testing were suggestive of probable OSAHS using the algorithms (p<0.0001).

Table 23: Comparison of subjective and objective measures of OSAHS prevalence. Comparison data unavailable for 21 participants. No significant difference was noted between genders (p=0.22).

		Objective OSAHS any		
		Yes	**No**	**Total**
Probable OSAHS any	**Yes**	38	27	65
	No	10	38	48
	Total	48	65	**113**

Table 24: Anthropometric characteristics of sleep study participants by presence or absence of OSAHS via objective sleep study. Chi-square test used for parametric categorical variables and t-test for continuous categorical variables. Values presented as mean±SD or n%.

*** OSAHS status could not be ascertained for 16 participants**

Characteristics	Total included	OSAHS positive n = 49 (37%) *		OSAHS negative n = 69 (52%) *		p
Age (years)	117	26 ± 9		25 ± 7		0.28
Gender (males : females)	118	34 : 15		36 : 33		0.09
Body Mass Index (kg/m^2)	101	30.2 ± 7.0		29.9 ± 5.8		0.84
Collar size (cm)	76	41.4 ± 7.9		40.3 ± 3.9		0.41
Comorbidities:						
Asthma	116	7	14.3%	9	13.4%	1.00
Hay fever	116	7	14.3%	15	22.4%	0.34
Thyroid problems	116	24	49.0%	16	23.9%	0.01
Epilepsy	116	3	6.1%	0	0.0%	0.07
Any adenoid and/or tonsil surgery	116	17	34.7%	11	16.4%	0.03
Any medication	116	40	81.6%	44	65.7%	0.06
Benzodiazepines	116	1	2.0%	0	0.0%	0.42
Antidepressants	116	2	4.1%	2	3.0%	1.00
Opiates	116	2	4.1%	0	0.0%	0.18
Oxygen	116	0	0.0%	1	1.5%	1.00
Melatonin	116	1	2.0%	0	0.0%	0.42
Antiepileptics	116	2	4.1%	2	3.0%	1.00
Contraceptives	116	3	6.1%	6	9.0%	0.73
Antihistamines	116	4	8.2%	5	7.5%	1.00

Table 25: Self-reported sleep and behaviour characteristics of sleep study participants by presence or absence of OSAHS. Chi-square test used for parametric categorical variables, t-test for continuous categorical variables and Mann-Whitney U test for non-parametric variables. Values presented as mean±SD, median(IQR) or n%.

*** OSAHS status could not be ascertained for 16 participants**

Sleep and behaviour characteristics	**Total included**	**OSAHS positive n = 49 (37%) ***		**OSAHS negative n = 69 (52%) ***		**p**
Developmental Behaviour Checklist for Adults (DBC-A):						
Disruptive behaviour subscale (scale range 0-34)	114	7 (4-12)		4 (1-10)		0.01
Mean item score (possible score 0-2)	114	0.41 (0.24-0.71)		0.24 (0.06-0.56)		0.01
Proportion of items checked (possible score 0-1)	114	0.35 (0.18-0.56)		0.24 (0.06-0.47)		0.03
Intensity index (possible score 0-1)	104	0.20 (0.00-0.40)		0.00 (0.00-0.15)		0.001
Anxiety/Antisocial subscale (scale range -2-14)	114	0 (-1-2)		0 (0-1)		0.91
Mean item score (possible score 0-2)	114	0.22 (0.11-0.44)		0.11 (0.00-0.22)		0.004
Proportion of items checked (possible score 0-1)	114	0.22 (0.11-0.33)		0.11 (0.00-0.11)		0.01
Intensity index (possible score 0-1)	84	0.27 (0.00-0.50)		0.00 (0.00-0.50)		0.33
Depressive subscale (scale range 0-18)	114	3 (1-6)		2 (0-5)		0.07
Mean item score (possible score 0-2)	114	0.33 (0.11-0.67)		0.22 (0.00-0.56)		0.07
Proportion of items checked (possible score 0-1)	114	0.22 (0.11-0.56)		0.22 (0.00-0.44)		0.12
Intensity index (possible score 0-1)	83	0.00 (0.00-0.38)		0.00 (0.00-0.19)		0.08
Pictorial Epworth Sleepiness Scale (pESS)	107	11 ± 6		7 ± 5		0.001
Pictorial Epworth Sleepiness Scale score >10	107	24	54.5%	11	17.5%	<0.0001
Snoring - *ever (≥1 night/week)*	113	*45*	*93.8%*	*51*	*78.5%*	-
Never		1	*2.1%*	11	*16.9%*	<0.0001
Rarely/sometimes (1-2 night/week)		7	*14.6%*	20	*30.8%*	
Often/frequent (≥3 nights/week)		38	*79.2%*	31	*47.7%*	
Don't know		*2*	*4.2%*	*3*	*4.6%*	-
Witnessed apnoeas - *ever (≥1 night/week)*	114	*20*	*40.8%*	*24*	*36.9%*	-
Never		7	*14.3%*	11	*16.9%*	0.02
Rarely/sometimes (1-2 night/week)		4	*8.2%*	15	*23.1%*	
Often/frequent (≥3 nights/week)		16	*32.7%*	9	*13.8%*	
Don't know		*22*	*44.9%*	*30*	*46.2%*	-

Nocturnal choking episodes - *ever (≥1 night/week)*	114	*21*	*42.9%*	*19*	*29.2%*	-
Never		17	*34.7%*	40	*61.5%*	0.001
Rarely/sometimes (1-2 night/week)		14	*28.6%*	19	*29.2%*	
Often/frequent (≥3 nights/week)		7	*14.3%*	0	*0.0%*	
Don't know		*11*	*22.4%*	*6*	*9.2%*	-
Frequent night wakenings - *ever (≥1 night/week)*	115	*38*	*79.2%*	*55*	*82.1%*	-
Never		7	*14.6%*	6	*9.0%*	0.15
Rarely/sometimes (1-2 night/week)		21	*43.8%*	40	*59.7%*	
Often/frequent (≥3 nights/week)		17	*35.4%*	15	*22.4%*	
Don't know		*3*	*6.3%*	*6*	*9.0%*	-
Unrefreshing sleep - *ever (≥1 night/week)*	115	*45*	*91.8%*	*52*	*78.8%*	-
Never		1	*2.0%*	11	*16.7%*	<0.0001
Rarely/sometimes (1-2 night/week)		10	*20.4%*	39	*59.1%*	
Often/frequent (≥3 nights/week)		35	*71.4%*	13	*19.7%*	
Don't know		*3*	*6.1%*	*3*	*4.5%*	-
Daytime sleepiness - *ever (≥1 night/week)*	115	*47*	*95.9%*	*49*	*74.2%*	-
Never		2	*4.1%*	17	*25.8%*	<0.0001
Rarely/sometimes (1-2 night/week)		17	*34.7%*	33	*50.0%*	
Often/frequent (≥3 nights/week)		30	*61.2%*	16	*24.2%*	
Don't know		*2*	*4.1%*	*3*	*4.5%*	-
Obstructive sleep apnoea (OSA) status:						
Prior diagnosis of OSA	116	6	12.2%	1	1.5%	0.04
Probable OSA using definition 1	113	36	75.0%	27	41.5%	0.001
Probable OSA using definition 2	113	38	79.2%	27	41.5%	<0.0001
Probable OSA using definition 3	113	36	75.0%	27	41.5%	0.001
Probable OSA on ≥1 definition	113	38	79.2%	27	41.5%	<0.0001

7.2.7 OSAHS severity

Differences in characteristics related to the objective severity of OSAHS are displayed in Table 26, Table 27, Table 28 and Table 29.

7.2.7.1 Anthropometric characteristics

No significant differences were noted in anthropometric measures or comorbidities or medications related to sleep using an AH cut-off of AH≥10 per hour in bed, the entry threshold for the treatment study, or an AH cut-off of AH≥25 per hour in bed, which is used clinically within the Department of Sleep Medicine, RIE, to diagnose OSAHS via a home sleep study. However, a trend was noted towards those with an AH≥25 per hour in bed being older (p=0.01), and to more males than females having an AH≥25 per hour in bed (p=0.03). Using an ODI cut-off of ODI≥10 as per the SIGN guidelines (Scottish Intercollegiate Guidelines Network 2003), no significant differences were noted, although there was a strong trend towards BMI being higher in with an ODI above the threshold (p=0.002).

7.2.7.2 Sleep symptoms

The prevalence of self-reported snoring was significantly higher in those with an AH≥10 per hour in bed (p<0.0001), with 64% reporting frequent snoring, and approached significance with thresholds of AH≥25 per hour in bed (74%; p=0.002) and ODI≥ 10 (74%; p=0.002) – see Table 27 . No significant differences were observed with any of the thresholds in terms of other symptoms including witnessed apnoeas, nocturnal choking, frequent night wakenings, unrefreshing sleep or daytime sleepiness.

Neither the total pESS score nor the proportion of participants with EDS differed significantly with an AH≥10, AH≥25 or ODI≥10, although there was trend towards higher pESS scores with an AH≥25 (p=0.04).

7.2.7.3 Behavioural and emotional disturbances

DBC-A subscale total scores, MIS, PIC and II did not differ significantly with an AH cut-off of AH≥10, AH≥25 or ODI≥10 (Table 27).

Table 26: Anthropometric characteristics of sleep study participants by severity of OSAHS, using AH cut-offs of ≥10/hr (CPAP trial entry point) and ≥25/hr (departmental clinical diagnostic threshold). Chi-square test used for parametric categorical variables and t-test for continuous categorical variables. Values presented as mean±SD or n%.

*** AH per hour in bed unavailable for 14 participants**

Characteristics	Total included	AH <10		AH ≥10		p	AH <25		AH ≥25		p
		n = 27 (20%) *		n = 93 (69%) *			n = 68 (51%) *		n = 52 (39%) *		
Age (years)	119	24 ± 8		26 ± 8		0.23	24 ± 6		27 ± 9		0.01
Gender (males : females)	120	11 :16		58 :35		0.05	33 : 35		36 : 16		0.03
Body Mass Index (kg/m^2) **	102	30.1 ± 5.5		30.2 ± 6.6		0.95	29.7 ± 5.9		30.8 ± 7.0		0.36
Collar size (cm)	76	40.4 ± 3.8		40.7 ± 4.4		0.84	40.0 ± 3.5		41.7 ± 5.1		0.09
Comorbidities:											
Asthma	118	3	12.0%	12	12.9%	1.00	7	10.6%	8	15.4%	0.58
Hay fever	118	5	20.0%	18	19.4%	1.00	14	21.2%	9	17.3%	0.65
Thyroid problems	118	6	24.0%	37	39.8%	0.17	24	36.4%	19	36.5%	1.00
Epilepsy	118	0	0.0%	3	3.2%	1.00	1	1.5%	2	3.8%	0.58
Any adenoid and/or tonsil surgery	118	3	12.0%	26	28.0%	0.12	12	18.2%	7	13.5%	0.09
Any medication	118	17	68.0%	71	76.3%	0.44	50	75.8%	38	73.1%	0.83
Benzodiazepines	118	0	0.0%	1	1.1%	1.00	1	1.5%	0	0.0%	1.00
Antidepressants	118	1	4.0%	3	3.2%	1.00	3	4.5%	1	1.9%	0.63
Opiates	118	0	0.0%	2	2.2%	1.00	1	1.5%	1	1.9%	1.00
Oxygen	118	0	0.0%	1	1.1%	1.00	1	1.5%	0	0.0%	1.00
Melatonin	118	0	0.0%	1	1.1%	1.00	0	0.0%	1	1.9%	0.44
Antiepileptics	118	1	4.0%	3	3.2%	1.00	3	4.5%	1	1.9%	0.63
Contraceptives	118	3	12.0%	6	6.5%	0.40	5	7.6%	4	7.7%	1.00
Antihistamines	118	3	12.0%	6	6.5%	0.40	5	7.6%	4	7.7%	1.00

Table 27: Self-reported sleep and behaviour characteristics of sleep study participants with severity of OSAHS. Chi-square test used for parametric categorical variables, t-test for continuous categorical variables and Mann-Whitney U test for non-parametric variables. Values presented as mean±SD, median(IQR) or n% unless otherwise stated.

*** AH per hour in bed unavailable for 14 participants**

Sleep and behaviour characteristics	Total included	AH < 10		AH > 10		p	AH < 25		AH > 25		p
		n = 27 (20%) *		n = 93 (69%) *			n = 68 (51%) *		n = 52 (39%) *		
Developmental Behaviour Checklist for Adults (DBC-A):											
Disruptive behaviour subscale (scale range 0-34)	115	6 (2-12)		5 (2-10)		0.96	5 (2-11)		6 (2-9)		0.69
Mean item score (possible score 0-2)	115	0.32 (0.12-0.69)		0.29 (0.12-0.59)		1.00	0.29 (0.12-0.66)		0.32 (0.12-0.54)		0.69
Proportion of items checked (possible score 0-1)	115	0.29 (0.12-0.56)		0.29 (0.12-0.47)		0.86	0.29 (0.12-0.59)		0.29 (0.12-0.47)		0.45
Intensity index (possible score 0-1)	105	0.00 (0.00-0.25)		0.00 (0.00-0.33)		0.52	0.00 (0.00-0.20)		0.13 (0.00-0.33)		0.09
Anxiety/Antisocial subscale (scale range -2-14)	115	1 (0-2)		0 (-1-1)		0.01	0 (0-2)		0 (-1-1)		0.05
Mean item score (possible score 0-2)	115	0.22 (0.00-0.44)		0.22 (0.11-0.33)		0.95	0.22 (0.00-0.44)		0.22 (0.11-0.33)		0.67
Proportion of items checked (possible score 0-1)	115	0.22 (0.00-0.42)		0.11 (0.11-0.22)		0.79	0.11 (0.00-0.33)		0.12 (0.11-0.25)		0.89
Intensity index (possible score 0-1)	84	0.00 (0.00-0.50)		0.00 (0.00-0.50)		0.48	0.00 (0.00-0.50)		0.20 (0.00-0.50)		0.39
Depressive subscale (scale range 0-18)	115	3 (0-5)		2 (1-5)		0.89	2 (0-5)		2 (1-4)		0.67
Mean item score (possible score 0-2)	115	0.28 (0.00-0.56)		0.22 (0.11-0.56)		0.88	0.22 (0.00-0.56)		0.22 (0.08-0.47)		0.67
Proportion of items checked (possible score 0-1)	115	0.28 (0.00-0.53)		0.22 (0.11-0.56)		0.95	0.22 (0.00-0.56)		0.17 (0.08-0.44)		0.47
Intensity index (possible score 0-1)	84	0.00 (0.00-0.33)		0.00 (0.00-0.25)		0.81	0.00 (0.00-0.25)		0.00 (0.00-0.36)		0.34
Pictorial Epworth Sleepiness Scale (pESS)	105	9 ± 7		9 ± 5		0.97	8 ± 5		10 ± 6		0.04
Pictorial Epworth Sleepiness Scale score >10	105	8	34.8%	27	32.9%	1.00	17	28.3%	18	40.0%	0.22
Snoring - *ever (≥1 night/week)*		*16*	64.0%	79	87.8%	-	52	80.0%	*43*	86.0%	-
Never	115	8	32.0%	5	5.6%	<0.0001	9	13.8%	7	14.0%	0.002
Rarely/sometimes (1-2 night/week)		8	32.0%	21	23.3%		23	35.4%	6	12.0%	
Often/frequent (≥3 nights/week)		8	32.0%	58	64.4%		29	44.6%	37	74.0%	
Don't know		*1*	4.0%	*6*	6.7%	-	*4*	6.2%	3	6.0%	-
Witnessed apnoeas - *ever (≥1 night/week)*		*7*	29.2%	38	41.3%	-	23	35.9%	22	42.3%	-
Never	116	3	12.5%	15	16.3%	0.24	11	17.2%	7	13.5%	0.57
Rarely/sometimes (1-2 night/week)		5	20.8%	14	15.2%		11	17.2%	8	15.4%	
Often/frequent (≥3 nights/week)		2	8.3%	24	26.1%		12	18.8%	14	26.9%	
Don't know		*14*	58.3%	39	42.4%	-	*30*	46.9%		0.0%	-

Nocturnal choking episodes - *ever (≥1 night/week)*			*7*	28.0%	*33*	36.3%	-	*23*	35.9%	*17*	32.7%	-	
Never			16	64.0%	42	46.2%		35	54.7%	23	44.2%		
Rarely/sometimes (1-2 night/week)	116		7	28.0%	26	28.6%	0.25	22	34.4%	11	21.2%	0.04	
Often/frequent (≥3 nights/week)			0	0.0%	7	7.7%		1	1.6%	6	11.5%		
Don't know			*2*	8.0%	*16*	17.6%	-	*6*	9.4%	*12*	23.1%	-	
Frequent night wakenings - *ever (≥1 night/week)*			*22*	88.0%	*72*	78.3%	-	*54*	83.1%	*40*	76.9%	-	
Never			1	4.0%	13	14.1%		5	7.7%	9	17.3%		
Rarely/sometimes (1-2 night/week)	117		17	68.0%	46	50.0%	0.18	36	55.4%	27	51.9%	0.31	
Often/frequent (≥3 nights/week)			5	20.0%	26	28.3%		18	27.7%	13	25.0%		
Don't know			*2*	8.0%	*7*	7.6%	-	*6*	9.2%	*3*	5.8%	-	
Unrefreshing sleep - *ever (≥1 night/week)*			*20*	80.0%	*78*	84.8%	-	*54*	83.1%	*44*	84.6%	-	
Never			4	16.0%	7	7.6%		6	9.2%	5	9.6%		
Rarely/sometimes (1-2 night/week)	117		13	52.0%	36	39.1%	0.06	32	49.2%	17	32.7%	0.10	
Often/frequent (≥3 nights/week)			7	28.0%	42	45.7%		22	33.8%	27	51.9%		
Don't know			*1*	4.0%	*7*	7.6%	-	5	7.7%	3	5.8%	-	
Daytime sleepiness - *ever (≥1 night/week)*			*17*	68.0%	*82*	89.1%	-	*52*	80.0%	*47*	90.4%	-	
Never			8	32.0%	9	9.8%		13	20.0%	4	7.7%		
Rarely/sometimes (1-2 night/week)	117		8	32.0%	45	48.9%	0.02	28	43.1%	25	48.1%	0.18	
Often/frequent (≥3 nights/week)			9	36.0%	37	40.2%		24	36.9%	22	42.3%		
Don't know			*0*	0.0%	*1*	1.1%	-	*0*	0.0%	*1*	1.9%	-	
Obstructive sleep apnoea (OSA) status:													
Prior diagnosis of OSA	118		1	4.0%	6	6.5%	1.00	1	1.5%	6	11.5%	0.04	
Probable OSA using definition 1	115		7	28.0%	54	60.0%	0.01	26	40.6%	35	68.6%	0.01	
Probable OSA using definition 2	115		7	28.0%	56	62.2%	0.003	27	42.2%	36	70.6%	0.003	
Probable OSA using definition 3	115		7	28.0%	54	60.0%	0.01	26	40.6%	35	68.6%	0.01	
Probable OSA on ≥1 definition	115		7	28.0%	56	62.2%	0.003	27	42.2%	36	70.6%	0.003	

Table 28: Anthropometric characteristics of sleep study participants by ODI. Chi-square test used for parametric categorical variables and t-test for continuous categorical variables. Values presented as mean±SD or n %.

*** ODI could not be ascertained for 20 participants**

Characteristics	Total included	ODI <10 n = 67 (50%) *		ODI ≥10 n = 47 (35%) *		p
Age (years)	113	24 ± 8		27 ± 7		0.05
Gender (males : females)	114	35 : 32		31 : 16		0.18
Body Mass Index (kg/m^2) **	100	28.4 ± 5.3		32.3 ± 6.8		0.002
Collar size (cm)	74	39.8 ± 3.5		41.5 ± 4.2		0.05
Comorbidities:						
Asthma	113	8	12.1%	10	21.3%	0.20
Hay fever	113	14	21.2%	13	27.7%	0.50
Thyroid problems	113	17	25.8%	21	44.7%	0.04
Epilepsy	113	0	0.0%	3	6.4%	0.07
Any adenoid and/or tonsil surgery	113	15	22.7%	16	34.0%	0.21
Any medication	113	42	63.6%	39	83.0%	0.03
Benzodiazepines	113	0	0.0%	1	2.1%	0.42
Antidepressants	113	3	4.5%	0	0.0%	0.27
Opiates	113	0	0.0%	2	4.3%	0.17
Oxygen	113	1	1.5%	0	0.0%	1.00
Melatonin	113	1	1.5%	0	0.0%	1.00
Antiepileptics	113	1	1.5%	3	6.4%	0.31
Contraceptives	113	1	1.5%	6	12.8%	0.02
Antihistamines	113	6	9.1%	3	6.4%	0.73

Table 29: Self-reported sleep and behaviour characteristics of sleep study participants by ODI. Chi-square test used for parametric categorical variables, t-test for continuous categorical variables and Mann-Whitney U test for non-parametric variables. Values presented as mean±SD, median(IQR) or n %.

*** ODI could not be ascertained for 20 participants**

Sleep and behaviour characteristics	**Total included**	**ODI <10**		**ODI ≥10**		**p**
		n = 67 (50%) *		**n = 47 (35%) ***		
Developmental Behaviour Checklist for Adults (DBC-A):						
Disruptive behaviour subscale (scale range 0-34)	111	4 (2-8)		7 (2-10)		0.21
Mean item score (possible score 0-2)	111	0.24 (0.12-0.47)		0.41 (0.12-0.60)		0.20
Proportion of items checked (possible score 0-1)	111	0.24 (0.12-0.41)		0.32 (0.12-0.53)		0.24
Intensity index (possible score 0-1)	101	0.00 (0.00-0.25)		0.11 (0.00-0.34)		0.26
Anxiety/Antisocial subscale (scale range -2-14)	111	0 (0-1)		0 (0-1)		0.93
Mean item score (possible score 0-2)	111	0.11 (0.00-0.39)		0.22 (0.11-0.44)		0.18
Proportion of items checked (possible score 0-1)	111	0.11 (0.00-0.28)		0.22 (0.11-0.33)		0.30
Intensity index (possible score 0-1)	81	0.00 (0.00-0.42)		0.10 (0.00-0.67)		0.15
Depressive subscale (scale range 0-18)	111	2 (0-5)		2 (1-4)		0.90
Mean item score (possible score 0-2)	111	0.22 (0.00-0.56)		0.22 (0.11-0.44)		0.86
Proportion of items checked (possible score 0-1)	111	0.22 (0.00-0.44)		0.22 (0.11-0.43)		0.93
Intensity index (possible score 0-1)	80	0.00 (0.00-0.25)		0.00 (0.00-0.25)		0.91
Pictorial Epworth Sleepiness Scale (pESS)	100	8 ± 5		9 ± 6		0.22
Pictorial Epworth Sleepiness Scale score >10	100	13	22.0%	14	34.1%	0.25
Snoring - *ever (≥1 night/week)*	110	*49*	*76.6%*	*42*	*91.3%*	-
Never		11	*17.2%*	2	*4.3%*	0.002
Rarely/sometimes (1-2 night/week)		20	*31.3%*	8	*17.4%*	
Often/frequent (≥3 nights/week)		29	*45.3%*	34	*73.9%*	
Don't know		*4*	*6.3%*	*2*	*4.3%*	-
Witnessed apnoeas - *ever (≥1 night/week)*	60	*22*	*33.8%*	*22*	*46.8%*	-
Never		11	*16.9%*	5	*10.6%*	0.29
Rarely/sometimes (1-2 night/week)		11	*16.9%*	8	*17.0%*	
Often/frequent (≥3 nights/week)		11	*16.9%*	14	*29.8%*	
Don't know		*32*	*49.2%*	*20*	*42.6%*	-

Nocturnal choking episodes - *ever (≥1 night/week)*	93	*24*	*36.4%*	*15*	*32.6%*	-
Never		35	*53.0%*	19	*41.3%*	0.13
Rarely/sometimes (1-2 night/week)		22	*33.3%*	10	*21.7%*	
Often/frequent (≥3 nights/week)		2	*3.0%*	5	*10.9%*	
Don't know		*7*	*10.6%*	*12*	*26.1%*	-
Frequent night wakenings - *ever (≥1 night/week)*	103	*53*	*81.5%*	*36*	*76.6%*	-
Never		6	*9.2%*	8	*17.0%*	0.45
Rarely/sometimes (1-2 night/week)		35	*53.8%*	22	*46.8%*	
Often/frequent (≥3 nights/week)		18	*27.7%*	14	*29.8%*	
Don't know		*6*	*9.2%*	*3*	*6.4%*	-
Unrefreshing sleep - *ever (≥1 night/week)*	112	*51*	*78.5%*	*41*	*87.2%*	-
Never		7	*10.8%*	4	*8.5%*	0.40
Rarely/sometimes (1-2 night/week)		26	*40.0%*	18	*38.3%*	
Often/frequent (≥3 nights/week)		25	*38.5%*	23	*48.9%*	
Don't know		*7*	*10.8%*	*2*	*4.3%*	-
Daytime sleepiness - *ever (≥1 night/week)*	113	*52*	*78.8%*	*42*	*89.4%*	-
Never		*14*	*21.2%*	4	*8.5%*	0.21
Rarely/sometimes (1-2 night/week)		29	*43.9%*	24	*51.1%*	
Often/frequent (≥3 nights/week)		23	*34.8%*	18	*38.3%*	
Don't know		*0*	*0.0%*	*1*	*2.1%*	-
Obstructive sleep apnoea (OSA) status:						
Prior diagnosis of OSA	113	2	3.0%	6	12.8%	0.07
Probable OSA using definition 1	111	27	42.2%	33	70.2%	0.004
Probable OSA using definition 2	111	28	43.8%	34	72.3%	0.004
Probable OSA using definition 3	111	27	42.2%	33	70.2%	0.004
Probable OSA on ≥1 definition	111	28	43.8%	34	72.3%	0.004

7.2.8 Relationship between sleepiness, objective sleep measures and behaviour

Bivariate correlation analysis was used to explore the relationships between sleepiness, objective sleep measures and behaviour. Generalized linear modelling was used to further explore the determinants of behaviour, sleepiness and home sleep study outcomes – see Table 30.

Associations between subjective sleepiness, as measured by pESS score, and increased total scores on the DBC Disruptive (ρ=0.382, p<0.0001) and Depressive (ρ=0.404, p<0.0001) subscales were noted, with weak but significant associations between pESS and Anxiety/Antisocial MIS (ρ= 0.255, p=0.05) and PIC (ρ=0.258, p=0.005) scores also evident. An increase in pESS was significantly associated with higher DBC-A Disruptive (β=0.31, p=0.03) and Depressive (β=0.12, p=0.03), but not Anxiety/Antisocial (p=0.18), subscale scores, controlling for age, gender and BMI. Higher pESS was also associated with higher BMI (ρ=0.277, p=0.005) and collar size (ρ=0.238, p=0.039), and lower mean oxygen saturation (ρ=-0.198, 0.047).

Transition index was related to higher intensity of problem behaviours (II) on the Anxiety/Antisocial (ρ=0.222, p=0.031) and Depressive DBC subscales (ρ=0.325, p=0.001).

BMI was associated with increased Anxiety/Antisocial behaviour (β=0.07, p=0.04), pESS (β=0.19, p=0.02) and ODI (β=0.81, p=0.01) scores, as well as a lower mean saturation (ρ=-370, p<0.0001), lower SpO2 nadir (ρ=-0.335, p=0.001) and higher mean desaturation (ρ==0.316, p=0.001).

Male gender was linked with a higher AH (β=16.34, p=0.01) and ODI (β=8.02, p=0.02) on the home sleep study. However, AH and ODI do not predict pESS or behaviour scores, and no other significant gender effects were noted.

Age did not demonstrate a significant effect on behaviour, sleepiness, AH or ODI in this population, although correlations with age and lower mean oxygen saturation (ρ=-0.385, p<0.0001) and larger mean desaturations (ρ=0.212, p=0.024) were noted.

Table 30: Determinants of subjective sleepiness, objective sleep measures and behaviour assessed by generalised linear modelling for continuous variables, controlling for age, gender, BMI, pESS, AH, ODI, DBC Disruptive, DBC Anxiety/Antisocial and DBC Depressive scores.

Variable	Total included	Determinants remaining in model	Estimate (β)	95% CI lower	95% CI upper	p
DBC-A Disruptive subscale total score	79	Age	-0.03	-0.25	0.19	0.81
		Gender (male)	0.25	-2.82	3.31	0.88
		BMI	0.06	-0.19	0.32	0.62
		pESS (self-rated)	0.31	0.04	0.58	0.03
		AH/hr in bed	-0.02	-0.08	0.04	0.57
		ODI	0.03	-0.09	0.15	0.62
DBC Anxiety/Antisocial subscale total score	79	Age	0.01	-0.05	0.07	0.76
		Gender (male)	0.35	-0.46	1.17	0.40
		BMI	0.07	0.01	0.14	0.04
		pESS (self-rated)	0.05	-0.02	0.12	0.18
		AH/hr in bed	0.00	-0.02	0.01	0.62
		ODI	-0.01	-0.04	0.02	0.57
DBC Depressive subscale total score	79	Age	0.00	-0.09	0.09	0.98
		Gender (male)	-0.66	1.89	0.565	0.29
		BMI	0.05	0.05	0.153	0.34
		pESS (self-rated)	0.12	0.02	0.233	0.03
		AH/hr in bed	-0.01	-0.04	0.01	0.29
		ODI	0.03	-0.02	0.08	0.21
pESS (self-rated)	101	Age	0.00	-0.13	0.13	0.98
		Gender (male)	1.08	-0.89	3.04	0.28
		BMI	0.19	0.03	0.35	0.02
		DBC Disruptive subscale total score	0.20	0.00	0.41	0.048
		DBC Anxiety/Antisocial subscale total score	-0.11	-0.76	0.53	0.73
		DBC Depressive subscale total score	0.35	-0.03	0.73	0.07
AH per hour in bed	90	Age	0.93	-0.05	1.90	0.06
		Gender (male)	16.34	3.68	28.99	0.01
		BMI	0.67	-0.37	1.74	0.22
		pESS (self-rated)	0.39	-0.84	1.61	0.54
		DBC Disruptive subscale total score	0.34	-0.91	1.59	0.59
		DBC Anxiety/Antisocial subscale total score	-1.98	-6.01	2.05	0.34
		DBC Depressive subscale total score	-0.79	-3.30	1.73	0.54
ODI	89	Age	0.41	-0.04	0.86	0.07
		Gender (male)	8.02	1.14	14.91	0.02
		BMI	0.81	0.24	1.38	0.01
		pESS (self-rated)	0.37	-0.32	1.05	0.30
		DBC Disruptive subscale total score	0.20	-0.50	0.89	0.58
		DBC Anxiety/Antisocial subscale total score	-1.66	-4.07	0.76	0.18
		DBC Depressive subscale total score	0.69	-0.89	2.27	0.39

7.3 Discussion

7.3.1 Acceptability of diagnostic test

Overall, the Embletta® Gold™ home sleep study equipment appears to be well accepted and effective in testing for OSAHS in the adult DS population. The majority of participants used the kit successfully, with only 10% of participants unable to obtain a study of sufficient quality to make a meaningful diagnosis. Most individuals managed to obtain a valid study after 1 or 2 nights, suggesting that a standard 2-night study as used in our trial is sufficient for the majority of DS adults. Only 6% required more than 2 nights to obtain a diagnosis. Although a "first-night effect" is well documented in the literature (Agnew et al. 1966; Toussaint et al. 1995; Scholle et al. 2003), this approach is not often adopted clinically due to financial and waiting time concerns, and there is also some evidence that multiple nights of recording are not required for the diagnosis of OSAHS in the majority of cases (Li et al. 2004; Ahmadi et al. 2009). Ambulatory testing at home may represent a significant cost saving over in-patient polysomnography, as demonstrated in studies in the general population (Dingli et al. 2003; J. F. Masa et al. 2011). A number of individuals (4% of those stating a reason) declined to participate in the sleep study due to being 'medical-phobic', having had numerous hospital procedures during their life, therefore home sleep studies may be more acceptable and appropriate in this group who may become anxious at the thought of attending hospital (Evans et al. 2005).

The families of 17% of responders who stated a reason declined to have a home sleep study due to the belief that the adult with DS for whom they care would be unable to tolerate the equipment or cope with the study; it is impossible to say whether this would have been the case or not, with the individual themselves having not been given the opportunity to try. Newer, smaller ambulatory sleep study devices are now available; a recent study in children with DS successfully used such equipment (Hill et al, personal communication re. UKCRN ID 14250), and future studies in adults with DS may recruit larger numbers of participants using similar, less intrusive equipment. Parental support and beliefs are known to have an effect on outcomes for the individual with ID (Cunningham 1996; Hassall et al. 2005), and so may be a

factor in the paucity of individuals with DS presenting at clinic; this is an area for further investigation.

7.3.2 Prevalence of OSAHS

In this study, 42% of individuals demonstrated a diagnosis of OSAHS via home polygraphy, much higher than the 2-4% prevalence reported in the general population (Young et al. 1993). This is lower than reported in previous studies in adults with DS using polysomnography, which have estimated prevalence at 83% (Resta et al. 2003) and 88% (Trois et al. 2009). However, both of these studies included a small number of individuals (n=6 and n=16 respectively), recruited from residential care home settings. As a community-based study of 134 individuals from across all four nations of the UK, our results may be more generalisable to the DS population as a whole. Baseline characteristics of participants undergoing home sleep study were broadly similar to those of the questionnaire study cohort as a whole, suggesting that this is a representative subset. However, the higher mean pESS score (9±6 v. 7±5) and higher percentage of probable OSAHS assessed by algorithm (56% v. 35%) in the sleep study group may indicate an element of selection bias.

Objective prevalence (42%) was similar to the subjective prevalence (35%) estimated via the questionnaire study. Comparison of these outcomes showed that the algorithms previously published by Furhmann et al (Fuhrman et al. 2012) have a good sensitivity and negative predictive value (79%), but a poor specificity and positive predictive value (58%). The algorithms are good at correctly identifying those with OSAHS, but perform less well in correctly identifying those without disease, and a high rate of false positives is evident – although 56% of our cohort had evidence of probable OSAHS using the algorithms, only 42% achieved a positive diagnosis via objective polygraphy. However, given the low rate of false negatives and a likelihood ratio of 1.9, our results suggest that screening for probability of OSAHS via questionnaire may be useful, particularly to allow a tentative diagnosis in individuals who may be intolerant of objective testing or in areas where access to sleep studies is limited. Prediction of OSAHS using subjective methods has been

shown to offer time and cost savings in individuals with high probability of OSAHS in the general population (Anttalainen et al. 2011).

7.3.2.1 Anthropometric data, comorbidities and medication

No significant differences were noted in terms of age, BMI, collar size, medication use or comorbidities between those with an objective diagnosis of OSAHS and those without.

In the general population, a gender effect is evident, with a male predominance of 2:1 noted (Young et al. 1993; Redline et al. 1994; Jordan & McEvoy 2003). Interestingly, no significant gender difference was noted in our group, despite a higher mean BMI in females. This suggests that other features related to DS may be more important than gender in the aetiology of OSAHS in this population. As discussed in Chapter 1, a raised BMI in females versus males with ID has been reported in the literature (Melville et al. 2005; Boyle et al. 2010).

It is possible that the absence of significant differences in outcomes between the OSAHS positive and OSAHS negative groups may be due to the use of home polygraphy rather than PSG. Studies have noted a dilution of the AHI when scoring home sleep studies versus polysomnography (Escourrou et al. 2015) due to limitations of the current international scoring rules, which require a measure of EEG arousal as part of the scoring criteria (Iber et al. 2007). It is important to bear in mind that the AH per hour in bed and the true AHI are not the same, and that accepted diagnostic thresholds, including the SIGN guidelines (Scottish Intercollegiate Guidelines Network 2003), are based on AHI on polysomnography. Our interpretation of the scoring rules, by scoring a reduction in airflow whether or not it is associated with an oxygen desaturation, with the assumption that there may have been an arousal, aimed to minimise the dilution effect. However, future studies should attempt to use PSG to more accurately quantify the severity of OSA in adults with DS; again, newer equipment which allows a limited PSG to be run at home with a minimum of extra sensors, may make this achievable. It may be that a higher AH threshold on home polygraphy is required, although using a cut-off of AH≥25 per

hour in bed, as used clinically within the Department of Sleep Medicine, and an ODI≥10 did not reveal any significant differences between groups.

It may be that, in adults with DS, multiple factors over and above age, gender and BMI influence the severity of OSAHS. These may include anatomical and physiological factors, such as anatomical variations in hard and soft tissue in the head and neck (Shott & Donnelly 2004; Shott 2006). Twice as many of those participants with an objective diagnosis of OSAHS had previously undergone tonsil/adenoid surgery (35%) compared with those who did not exhibit OSAHS on their sleep study (16%), though this did not reach significance using our stringent criteria (p=0.03). This suggests that adenotonsillectomy in childhood may not provide lasting resolution of OSAHS in this group, although, as discussed in Chapter 5, selection bias due to previous diagnosis and surgical treatment of OSAHS cannot be ruled out. Nevertheless, a prospective study of the long-term efficacy of adenotonsillar surgery in individuals with DS would be of interest. Although a number of studies have examined the effects of adenotonsillectomy in children with and without DS (Chervin et al. 2006; Mitchell 2007; Rogers et al. 2009; Shete et al. 2010; Bhattacharjee et al. 2010; Rosen et al. 2011; Thottam et al. 2015), none of these have assessed long-term benefit. Indeed, the recent CHAT study, which assessed neurocognitive performance before and after adenotonsillectomy in typically-developing children (Marcus et al. 2013) followed up participants for only 7 months postoperatively.

7.3.2.2 Sleepiness, behavioural and emotional disturbances

Although behaviour scores did not differ significantly between those with and without a diagnosis of OSAHS using our strict criteria, there was a trend towards more disruptive behaviour in the OSAHS group, which may have been limited by the relatively small numbers in each group. Higher pESS scores were significantly associated with higher scores in the Disruptive and Depressive domains of the DBC-A. Sleep fragmentation was weakly associated with increased intensity of Anxiety/Antisocial behaviour. Although not reaching significance, these results support previous reports of behavioural disturbances related to OSAHS and other sleep disturbances in individuals with DS (Brylewski & Wiggs 1999; Capone et al.

2006; Dykens 2007). Behavioural problems in individuals with ID, including DS, have been associated with living in a residential care setting (Jones et al. 2008), and it has been suggested that challenging behaviour is a factor in individuals being moved from family to residential care (Oakes 2012). Behaviour changes can also be viewed as a marker of the early stages of dementia in adults with DS (Ball et al. 2006). Given these potentially major implications, it is important that other reasons for behavioural disturbance, such as OSAHS, are investigated. It is likely that treatment of OSAHS may improve behaviour in this group, and this is explored further in Chapter 8.

7.4 Conclusion

This first large survey of objective prevalence of OSAHS in adults with DS suggests that 42% of this population may have the disorder. Subjective assessment of probable risk of OSAHS using questionnaire data is useful in this group. A trial of the effects of treatment on OSAHS in adults with DS was warranted on the basis of these findings, and this is the focus of Chapter 8 of this thesis.

Chapter 8: Treatment study

This chapter describes the treatment phase of the study: a randomised, controlled trial of CPAP therapy versus conservative lifestyle advice.

8.1 Methods

8.1.1 Treatment study invitation

All participants meeting inclusion criteria after successful completion of a home sleep study were invited to participate in the treatment phase of the study.

Once their sleep study had been scored by an RPSGT and reviewed by a sleep physician, as per Chapter 7, all participants were sent written confirmation of their home study results. The results letter (see Appendix 2) included details of their AH and ODI, as well as their eligibility for further participation. In those participants eligible for the treatment study, the results letter was followed up by a phone call from the investigator to discuss the results as required and to schedule an appointment for the baseline visit.

8.1.2 Inclusion criteria

The inclusion criteria for the treatment phase of the study were as follows:

- A clinical diagnosis of DS.
- Age ≥16 years.
- A clinical diagnosis of OSAHS, defined as AH ≥ 10 events per hour on multichannel sleep study **and** symptoms of excessive daytime sleepiness or pESS ≥9.
- Ability to give informed consent and comply with protocol (participant or welfare guardian/attorney, as appropriate).

The age of legal capacity in Scotland is 16 years (Scottish Government 1991). Although the legal age of adulthood is 18 across the rest of the UK, consenting

participants aged ≥16 years were enrolled in the study, regardless of their country of residence.

The clinical diagnosis of DS including results of karyotyping were confirmed verbally with the participant's relative/carer.

Liberal OSAHS diagnostic criteria were set for this study. It is possible that adults with DS who already have a degree of cognitive impairment may be more sensitive to the effects of mild OSAHS or SDB, and so we were keen to include these participants in the study to assess their response to CPAP treatment. As discussed in Chapter 2, the standard threshold for OSA diagnosis of OSA is an AHI of ≥5 events per hour of sleep on PSG, with an AHI of 5-14 rated as mild, 15-30 as moderate and >30 as severe OSA (Scottish Intercollegiate Guidelines Network 2003; Epstein et al. 2009). Clinically, treatment with CPAP is usually indicated in symptomatic patients with an AHI ≥15. The literature generally states that there is a dilution of AHI when using limited cardio-respiratory studies, related to two main factors: the absence of a valid measure of sleep/wake resulting in calculation of the number of events per hour using hours in bed rather than hours of sleep; and the absence of a valid measure of EEG arousal, resulting in systematic underscoring when using the recognised standard scoring criteria (Collop et al. 2007; Epstein et al. 2009; Hedner et al. 2011). However, in our clinical experience, our in-house interpretation of the AASM2007 scoring criteria for use when scoring limited sleep studies may also result in over-scoring of breathing events due to the inclusion of events without associated oxygen desaturation which may not have an associated arousal. Clinically, to compensate for the possible disparity between AH and AHI, we use a higher diagnostic threshold of ≥25 events per hour of sleep on a limited study, with patients in the "grey area" below this threshold typically going on to have a full PSG study.

Although a pESS ≥10 is generally considered abnormally sleepy in the general adult population, this subjective rating scale can be underscored or misinterpreted, and can often be underestimated due to situation-specific issues resulting in omission of particular questions; for example, if an individual does not drive, they may omit or under-score the driving-related questions, reducing their overall score. Therefore, in

this study, a conservative pESS of ≥9 was used. In the event of an pESS <9, other symptoms of excessive daytime sleepiness were also acceptable, for example unrefreshing sleep or daytime sleepiness reported to occur at least once per week on the prevalence questionnaire. See Chapter 5 for a discussion of issues with the use of the pESS in this population

As discussed in Chapter 4, ethical approval was initially only given for inclusion of adults with capacity to give consent for themselves. However, from March 2013, AWI were also eligible to participate, with consent given on their behalf by their nearest relative or welfare guardian.

Those not fulfilling the inclusion criteria were withdrawn from the study, and were integrated into the normal clinical pathways of the Department of Sleep Medicine or referred to their local sleep centre as appropriate.

8.1.3 Exclusion criteria

The exclusion criteria for the treatment phase of the study were as follows:

- Previous exposure to CPAP therapy.
- Arterial oxygen saturation <90% on room air.
- Participants with chronic heart failure or recent myocardial infarction.
- Participants with known moderate or severe dementia.
- Participants with severe behavioural problems that would preclude sleep studies or CPAP treatment.
- Inability to comply with the protocol.

CPAP-naïve participants were enrolled in the study; individuals currently using CPAP or who had previously been successfully established on CPAP for at least 2 weeks were excluded. Individuals who had tried CPAP but who were not established remained eligible.

Awake arterial oxygen saturation on room air was assessed using the oximetry trace of the home sleep study. Medical history was discussed verbally with the participant and their relative/carer prior to study entry.

Although the study procedures were designed to be accessible to participants with as broad a range of abilities as possible, any individuals whose disabilities or behavioural problems would preclude the collection of useful data were excluded from participation. To allow inclusion of as many participants as possible, travel expenses were paid for all study-related hospital visits. Home visits were offered to any willing participants whose mobility or transport availability meant they were unable to attend appointments at the Royal Infirmary of Edinburgh.

Initially, FEV_1 <60% was included as an exclusion criterion. However, significant problems were encountered in conducting spirometry testing with adults with DS. Many participants had not had lung function tests prior to enrolment, and conducting spirometry at baseline proved difficult. This was discussed with Dr Andy Robson, Senior Clinical Scientist at the Respiratory Function Department, Royal Infirmary of Edinburgh. Dr Robson advised that people with learning disabilities often had problems complying with spirometry test instructions, and that no specific protocol or advice to improve this was available. On discussion with the Principal Investigator, Dr Renata Riha, Consultant in Sleep and Respiratory Medicine, it was felt that this exclusion criterion could be omitted without any detriment to participants.

8.1.4 Blinding

This was a single-blind study. All study-specific procedures at visits 2, 5, 6 and 7 were completed by a blinded investigator. The randomisation procedure and all subsequent treatment-related procedures, including visits 3 and 4a, were completed by a non-blinded investigator. Since only participants in the lifestyle group required visit 4b, this visit was conducted by a second blinded investigator to maintain the blinding status of the first blinded investigator. As far as possible, the same second blinded investigator conducted visit 4 to minimise inter-rater variability.

8.1.5 Recording and storage of study data

All study data and study-related documents were stored within case report files (CRFs). Three CRFs were used per participant: a blinded CRF, containing the home sleep study report, anthropometric assessments, cognitive function tests results and

completed questionnaires from all visits except visit 3, 3a, 4, 4a and 4b and copies of study-related correspondence; an unblinded CRF, containing treatment-related information from all visits including CPAP download reports, the monthly diaries and any other treatment-related correspondence; and a second unblinded CRF, containing the cognitive test results and questionnaires from visits 4 and 4a. All CRFs were stored securely in lockable filing cabinets within the Department of Sleep Medicine, which is a restricted-access area controlled by proximity card.

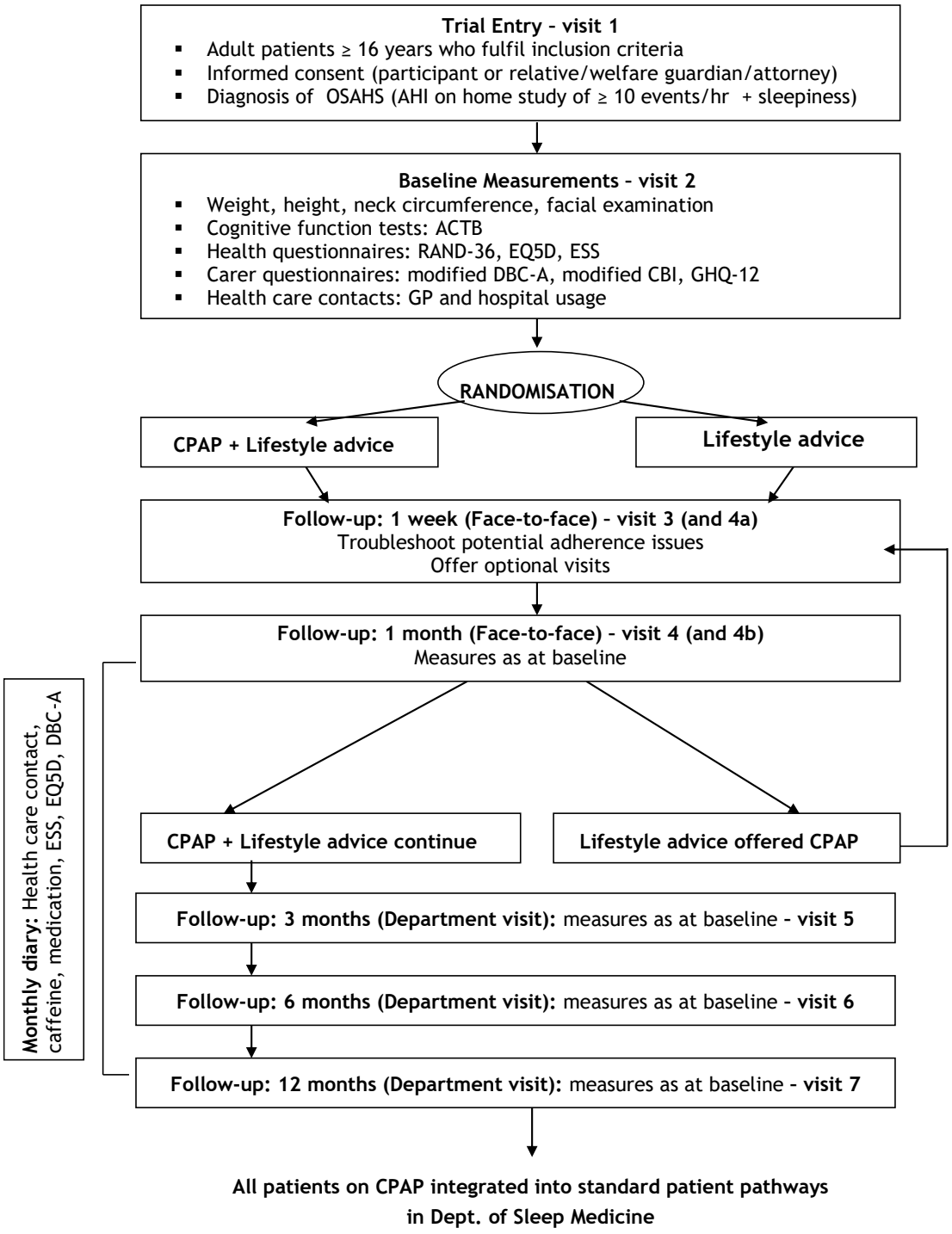
Hospital casenotes were recalled for any participant who was already registered as an NHS Lothian patient. Copies of study-related documents and correspondence were filed and patient interactions were documented in the casenotes as required.

8.1.6 Study visit schedule

The study visit schedule is shown in Figure 23. All study visit dates were agreed at the baseline visit where possible. All visits were scheduled based upon the date of the baseline visit, i.e. 1 month from baseline, 3 months from baseline etc. Visits were booked as close to the expected date as possible; however, a tolerance of one week either side of the expected date was allowed for visits up to 3 months, and 2 weeks either side for visits after 3 months to accommodate staff and participant availability Visits which were cancelled for any reason were rescheduled within the same tolerance limits as far as possible.

Participants were asked to attend all appointments with a relative/carer who knew them well, and to attend with the same relative/carer on every occasion, as far as possible, to minimise inter-rater variability in questionnaire completion. In the event of a different carer attending, the relative/carer questionnaire for that visit was sent to the usual carer for completion and return by post.

Figure 23: Flow diagram of CPAP evaluation phase of study: trial entry, randomisation, treatment arms and follow-up schedule.



8.1.7 Baseline visit (Visit 2)

Participants fulfilling the inclusion criteria attended a baseline visit, either in hospital or at home. Baseline measurements and procedures are detailed below. This visit took approximately 1.5hr to complete, although up to 3 hours was allocated to allow for variations in participants' level of ability.

8.1.7.1 Anthropometric data

Height, weight, neck circumference and craniofacial features (presence of macroglossia, gothic palate, adenoid facies, malocclusion and tonsillar enlargement) were assessed using standardised techniques.

8.1.7.1.1 Body mass index

The participant's height (m) and weight (kg) were measured, fully clothed but without shoes. Body mass index (BMI) was calculated in kg/m^2 using these measurements. Although gender-specific percentile growth charts for children with DS are available (McGowan et al. 2012), BMI norms for adults with DS are not; BMI was classified using the standard World Health Organisation International Classification of adult underweight, overweight and obesity according to BMI (World Health Organization 2006):

- $<18.50kg/m^2$ = underweight
- $18.50\text{-}24.99kg/m^2$ = normal
- $25.00\text{-}29.99kg/m^2$ = overweight
- $30.00\text{-}34.99kg/m^2$ = obese class I
- $35.00\text{-}39.99kg/m^2$ = obese class II
- $\geq 40kg/m^2$ = obese class III.

WHO BMI categories are applicable to individuals aged ≥19 years only.

8.1.7.1.2 Neck circumference

The participant's neck circumference (cm) was measured using a soft, flexible measuring tape, with the participant in the standing position. Neck circumference corrected for height has been shown to be a useful predictor of OSA, more so than general obesity(Davies & Stradling 1990; Davies et al. 1992).

8.1.7.1.3 Macroglossia

Individuals with DS frequently show evidence of relative, rather than true, macroglossia; that is, the tongue appears large relative to the size of the oral cavity (Guimaraes, Donnelly et al. 2008). Participants were asked to open their mouth, and a subjective assessment of tongue size was made by the investigator, using the clinical features described by Vogel et al (Vogel et al. 1986) .

8.1.7.1.4 Gothic palate

A high, vaulted or "gothic" palate has been reported in adults with DS (Panchón-Ruiz et al. 2000; Dellavia et al. 2007). Subjective assessment of the presence of a high, arched palate was made by the investigator.

8.1.7.1.5 Adenoidal facies

The characteristic appearance of a pinched nose, nasal congestion and mouth breathing during wakefulness is known as adenoidal facies (Quick & Gundlach 1978). Often seen in conjunction with a gothic palate, adenoidal facies can be an indicator of nasal airway obstruction. Again, subjective assessment of the presence adenoidal facies was made by the investigator.

8.1.7.1.6 Malocclusion

A subjective assessment of each participant's tooth alignment was made by asking the participant to open their mouth and then bite together. Occlusion was rated as normal, slight overbite (class I malocclusion), retrognathia (class II malocclusion) or prognathia (class III malocclusion); see Figure 24.

8.1.7.1.7 Mallampati score

A subjective assessment of Mallampati score (Mallampati et al. 1985) was made by the investigator. This scale, which rates crowding of the oropharynx based on visibility of the tonsillar pillars, soft palate and uvula (see Figure 25), was originally developed as a method of predicting patients at risk of difficult intubation under anaesthetic. However, it has since been shown to be of clinical value in assessment of SDB, with Mallampati score significantly associated with both presence and severity of OSA in individuals with a high clinical suspicion of OSA (Nuckton et al. 2006).

Figure 24: Assessment of dental occlusion: (A) Normal occlusion; (B) Class I malocclusion; (C) Class II malocclusion; (D) Class III malocclusion. From: Dorland's Medical Dictionary for Health Consumers © 2007 by Saunders, an imprint of Elsevier, Inc. Used with permission.

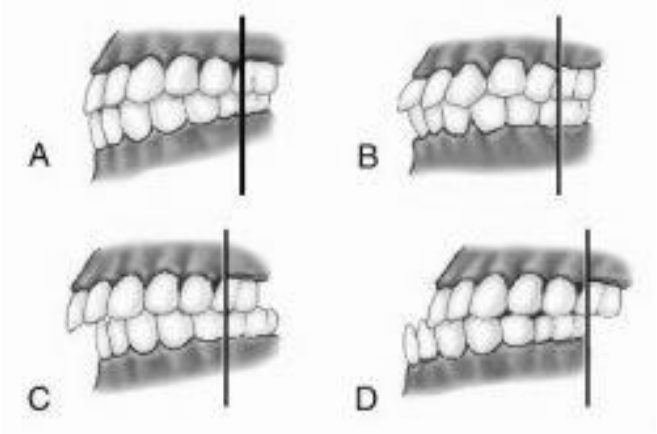
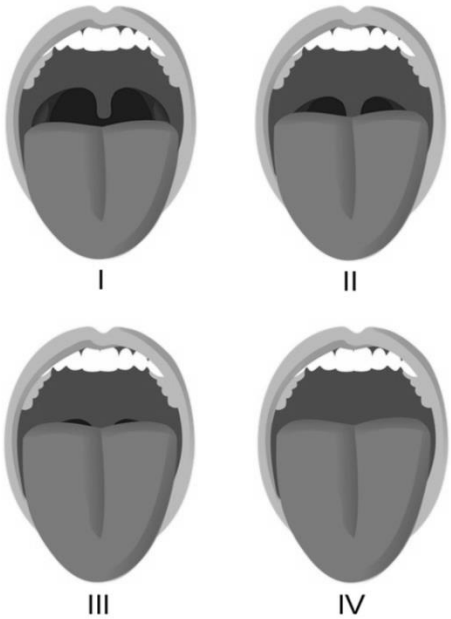


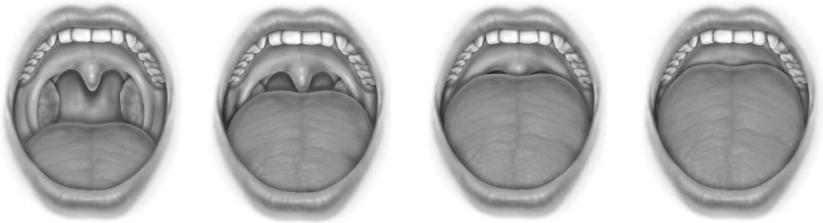
Figure 25: Mallampati score, rating crowding of the oropharynx based on visibility of the tonsillar pillars, soft palate and uvula. Author Jmarchn, January 29, 2011. Permission is granted to copy, distribute and/or modify this document under the terms of the GNU Free Documentation License, Version 1.2 or any later version published by the Free Software Foundation.



8.1.7.1.8 Friedman score

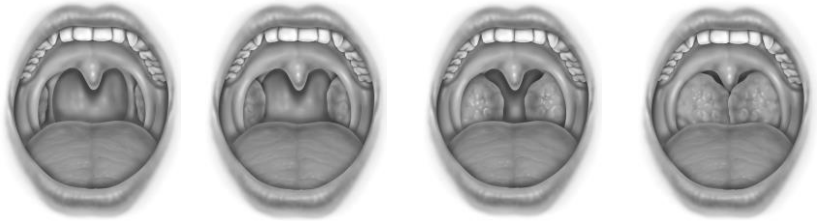
The Friedman score (Friedman et al. 2002) was originally developed as a predictor of successful uvuolpalatopharyngoplasty (UPPP) in patients with SDB. This staging system uses assessment of palate position and tonsillar size, combined with BMI, to give a score of I to III (see Figure 26).

Figure 26: Friedman scale. Originally developed to predict surgical success, this rating system combines palate position, tonsillar size and body mass index to give a rating of oropharyngeal crowding. Adapted from Friedman 2002, with permission, Sage publications.



I **II** **III** **IV**

Friedman palate position



I **II** **III** **IV**

Friedman tonsil position

	Palate position	**Tonsil size**	**Body mass index (kg/m^2)**
Stage I	1 2	3, 4 3, 4	<40 <40
Stage II	1, 2 3, 4	0, 1, 2 3, 4	<40 <40
Stage III	3 4 Any	0, 1, 2 0, 1, 2 Any	<40 <40 >40

8.1.7.2 Cognitive function tests

Cognitive function was assessed using tests from the Arizona Cognitive Test Battery (ACTB) - a set of computer-based tests developed specifically to assess cognitive function and dysfunction in adults and children with DS (Edgin et al. 2010). Data suggests that this collection of measures is well suited for outcome studies in this patient group, with few participants unable to complete the tasks and low levels of floor effects (where tests are too difficult to perform and so do not provide a meaningful measure). Importantly, the tests have been validated for use in both laboratory and home settings, with no significant differences in outcomes.

Following discussion of the design of this study with Professor Lynn Nadel of the Down Syndrome Research Group at the University of Arizona, whose team developed and validated the ACTB, the following subset of ACTB tests was used:

- Kaufman Brief Intelligence Test 2nd edition (KBIT-2) – to assess background performance level.
- Scales of Independent Behaviour Revised (SIB-R) – parent/carer rating of problem behaviours and their severity.
- CANTAB paired associates learning (PAL) – measuring hippocampal function.
- CANTAB simple reaction time (SRT) – measuring cerebellar function.
- Modified DOTS test (Frogs & Cats) – measuring prefrontal function.

These measures were chosen to be as concise as possible whilst still including a measure of the function of the brain region which are known to be most affected in individuals with DS and in OSAHS, and so are potentially most likely to benefit from improvement in sleep architecture and oxygenation (see Chapters 1-3). The complete battery took approximately 45min to complete. Testing was conducted at the same time (early to mid-afternoon) on every visit for all participants to minimise circadian effects on performance (Schmidt et al. 2012).

8.1.7.2.1 KBIT-2

The Kaufmann Brief Intelligence Test Version 2, or KBIT-2 (Pearson Clinical Assessment, San Antonio, TX, USA), is a validated instrument, suitable for individuals aged 4-90 years, providing a quick and reliable measure of verbal and non-verbal intelligence. The test is administered using a full-colour flipchart, and comprises 3 parts: Verbal Knowledge, Matrices and Riddles. Each section is scored individually. Scores on the Verbal Knowledge and Riddles sections are combined to give a Verbal score, which tests crystallised ability. The Matrices test gives a Nonverbal score, measuring fluid reasoning. The Verbal and Nonverbal scores are then combined to give an overall score, the IQ Composite. Normative data, based on the US population, is provided for both the Verbal and Nonverbal domains, as well as the IQ Composite. The test has been specifically validated in adults and children with intellectual disability, and has been shown to be perform effectively in this group despite low mean IQ scores (Kaufman & Kaufman 2004). The KBIT-2 correlates well with a number of other standard measures of cognitive ability and IQ, including the Wechsler Abbreviated Scale of Intelligence (WASI) and Wechsler Adult Intelligence Scale – 3rd Edition (WAIS-III) (Kaufman & Kaufman 2004).

The Verbal Knowledge subtest is comprised of 60 multiple-choice items measuring vocabulary and general knowledge about the world, covering a number of areas including nature, geography, science and the arts. The examiner asks the question verbally and the individual points to the correct picture from a selection of 6 pictures shown. Two types of item are presented in this subtest: questions assessing receptive vocabulary (e.g. “Point to money”, “point to elderly”) and questions examining general information (“Point to the one that goes with thunder”, “Point to a famous building in India”).

The Matrices subtest has 46 multiple-choice items, assessing the participant’s reasoning and problem-solving ability. These include meaningful stimuli such as everyday objects and people, as well as abstract signs and symbols. The early items ask which picture goes best with a stimulus picture, e.g. a car goes with a truck, a fishbowl goes with a fish. Later items can be meaningful or abstract, and ask which picture best completes an analogy, e.g. a boat goes with the sea, just as a car goes

with a road; a square with a circle inside goes with an empty square, just as a triangle with a circle inside goes with a triangle. The final matrices require the participant to select the missing symbol from a matrix of 4 or 9 symbols.

The Riddles subtest has 48 items assessing verbal comprehension, reasoning and vocabulary. The examiner asks a question, and the participant has to either point to the picture that shows the best answer or verbally provide a single-word answer. From item 9 onwards, no picture stimuli are provided. Early questions contain 2 clues (e.g. “Point to something you can ride in that floats”, “Point to something that squeaks and has a skinny tail”), with later questions providing 3 (e.g. “What has a checkout desk, places to read and rows of books?”, “What melts, burns and is made of wax?”).

The KBIT-2 is particularly useful for testing persons with ID. Questions are administered using only spoken word and pictures, allowing it to be used with individuals who cannot read. Answers in the Verbal Knowledge and Matrices tests, and in the early part of the Riddles test, are indicated by pointing, allowing testing of persons without speech. The test allows teaching during administration, so the examiner can rephrase a question or use sign and gesture to help individuals understand the instructions more clearly, ensuring valid testing of persons with ID.

The KBIT-2 is designed to be administered starting from the individual’s age range, dropping back a start point if the individual gets any of the first 3 questions at their start point wrong. The process of dropping back a start point continues until the individual correctly answers the first 3 questions of a point or start point 1 is reached. However, for ease of administration and to avoid unnecessary frustration for adults with DS with significant ID, all subtests were administered from question 1 in this study. Questions were presented in stepwise order, with each subtest discontinued upon 4 consecutive incorrect answers being given at any point after the individual’s age-designated start point. Depending on the participant’s level of ability, the test took 20-40 minutes to administer.

The KBIT-2 test was scored manually using the standard instructions, giving raw scores for the verbal (maximum possible score =108) and non-verbal (maximum possible score =46) domains (Kaufman & Kaufman 2004).

8.1.7.2.2 SIB-R

The Scales of Independent Behaviour - Revised, or SIB-R (Riverside Publishing Company, Rolling Meadows, IL, USA), is a standardised tool for assessment of skills required for everyday independent living, administered to the participant's relative/carer and validated in individuals aged 3 month to 90 years. The full scale comprises 259 items measuring broad independence. These items are divided into 14 subscales, covering a diverse range of areas including gross- and fine-motor skills, language expression and comprehension, use and understanding of money, toileting, domestic skills, work skills and timekeeping. The subscales are then grouped into 4 adaptive behaviour clusters: Motor Skills, Social Interaction and Communication Skills, Personal Living Skills and Community Living Skills.

Different forms of the test can be used, including the Full Scale, Short Form and Early Development Form, and these can be administered either by structured interview or by checklist administration, where the relative/carer marks the answers themselves in the response booklet. All forms of the test are administered alongside the Problem Behavior Scale, which gives an overview of 8 types of problem behaviour (Hurtful to Self, Unusual or Repetitive Habits, Withdrawal or Inattentive Behaviour, Socially Offensive Behavior, Uncooperative Behavior, Hurtful to Others, Destructive to Property, Disruptive Behavior) which can then be grouped into 3 Maladaptive Behavior groups (Internalized, Asocial and Externalized). The relative/carer is asked to state whether the individual exhibits each type of behaviour and, if so, describe the behaviour and, using Likert-type scales, rate its frequency (1 = less than once a month to 5 = 1 or more times an hour) and severity (0 = not serious to 4 = extremely serious).

In this study, the Short Form was used via checklist administration, along with the Problem Behavior Scale, providing a brief evaluation of participants and taking

around 20 minutes to complete. Time was taken to instruct the relative/carer in the correct use of the SIB-R questionnaire at the first visit.

The SIB-R Short Form is uses 40 items from across the 14 subscales of the Full Scale. For each item, the relative/carer is asked to rate the participant's ability ("Does (or could do) the task completely, without help or supervision") on a Likert-type scale: 0 = Never or rarely, even if asked; 1 = Does, but not well or about ¼ of the time, may need to be asked; 2 = Does fairly well or about ¾ of the time, may need to be asked; 3 = Does very well, always or almost always, without being asked. Item scores are summed to give a total raw score from a possible total of 120 (Bruininks et al. 2006).

8.1.7.2.3 CANTAB PAL

The Cambridge Neuropsychological Test Automated Battery (CANTAB; Cambridge Cognition Ltd., Cambridge, UK) is a suite of highly validated cognitive function tests (>1600 peer reviewed papers; www.camcog.com), covering a range of neuropsychological functions associated with different brain regions. All tests are visual, using abstract shapes and symbols, allowing the tests to be used and compared regardless of language, culture or literacy level. Tests are interactive and presented via a touch screen.

The Paired Associates Learning task (CANTAB PAL) is a test of hippocampal function, spatial associative memory (Swainson et al. 2001), which was selected for inclusion in the ACTB on the basis of previous studies which showed impairment in this area in individuals with DS (Pennington 2009; Visu-Petra et al. 2007). In this test, 6 white boxes are displayed in a circle on the screen. Each box "opens up" one at a time to show its contents, then closes again, with one of the boxes containing an abstract figure. Once all the boxes have displayed their contents, the figure appears in the centre of the screen and the participant must touch the box containing the figure. The test increases in complexity with each correct answer, from one, to two, then three figures to remember, then six or eight boxes containing a figure. The test ends once the eight-box stage is completed successfully, or after ten incorrect attempts.

The test is scored automatically by the CANTAB software, and a standard report produced. The outcome measures used were the number of attempts required to obtain a correct answer (mean errors to success – range 0-9) and the number of trials completed correctly at the first attempt (first trial memory score – range 0-26) .

Figure 27: CANTAB Paired Associates Learning. The content of each box is displayed in turn (left); the participant must then touch the box in which the figure shown in the centre of the screen was located (right). From Cantab Research Suite 6 Test Administration Guide Version 6.0.0, Cambridge Cognition Ltd., 2014. Used with permission.

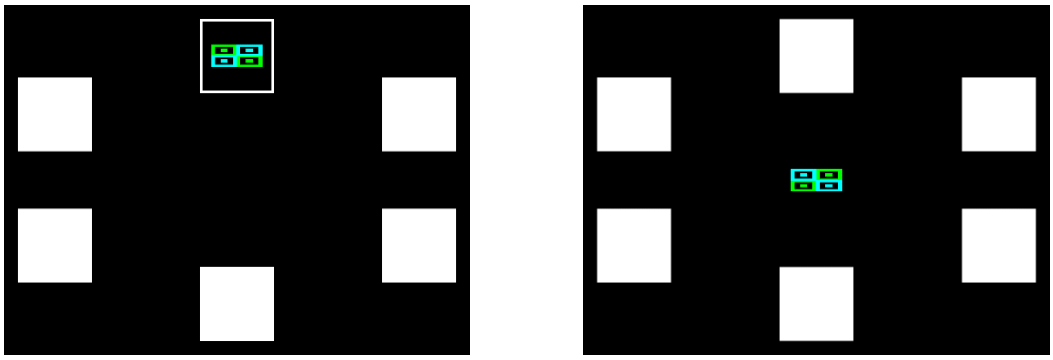
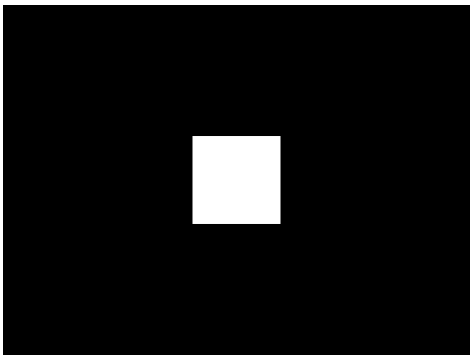


Figure 28: CANTAB Simple Reaction Time – the participant must press a button on a press-pad as quickly as they can when the white square is displayed. From Cantab Research Suite 6 Test Administration Guide Version 6.0.0, Cambridge Cognition Ltd., 2014. Used with permission.



8.1.7.2.4 CANTAB SRT

The CANTAB Simple Reaction Time test (CANTAB SRT) is a measure of cerebellar function, specifically motor response time and attention (Allen 1997). A white square is presented on the screen, and the participant must respond by pressing a button on a press pad as quickly as possible. The delay between stimuli presentation varies throughout the test. Twenty-four practice trials are presented, prior to two blocks of 50 test trials. The outcome measure for this test is the mean latency of correct responses in milliseconds.

8.1.7.2.5 Modified Dots task – Frogs and Cats

The Dots task (Davidson et al. 2006) is a measure of prefrontal function, specifically working memory and inhibitory control, which is suitable for individuals aged ≥4 years.

A modified version of the Dots task was provided by the Down Syndrome Research Group, Department of Psychology, University of Arizona, running on the Presentation platform (Neurobehavioral Systems Inc., Berkeley, CA, USA). Entitled Frogs and Cats, this task has two training phases and one testing phase. The first learning phase involves the display of a picture of a cat on the left or right side of a touch screen, which the participant must respond to by pressing a button on screen beneath the picture “because cats like to curl up and sleep and stay still” (congruent phase). Next, a picture of a frog is displayed on the left or right of the screen, to which the participant must respond by pressing a button on the opposite side of the screen, “because frogs like to hop over to the other side” (incongruent phase). The test phase involves the display of frogs and cats in a random order, with the participant responding using the congruent or incongruent rule as appropriate.

This test was scored on behalf of the investigators by Goffredina Spanò, Department of Psychology, University of Arizona. The outcome measures for this test are the percentage of correct responses for the congruent, incongruent and testing phases.

8.1.7.3 Health & sleepiness questionnaires

A series of questionnaires assessing the participant's subjective sleepiness and general health and wellbeing were completed at baseline, 1 month, 3 months, 6 months and 12 months:

- EQ-5D
- RAND-36
- Epworth Sleepiness Scale (ESS)
- Questions regarding healthcare contact, caffeine intake and medication use

The questionnaires were printed using a minimum 14-point font for accessibility to participants who may have visual impairment. However, the wording of the standard instruments (EQ-5D, RAND-36, pESS) could not be simplified without compromising the validity of the measures; therefore, many participants required their relative/carer's assistance with completion of these questionnaires. Easy-read language was used wherever possible elsewhere in the questionnaire, including the healthcare use and caffeine/medication use sections.

8.1.7.3.1 EQ-5D

The EQ-5D questionnaire is a standardised measure of health status and economics (The EuroQol Group 1990). The 2-page questionnaire is designed to be self-completed, and is written in simple language for ease of use. It can be quickly scored to give two standardised outcome measures (The EuroQol Group 2010). The first page of the questionnaire consists of five multiple-choice questions, answered via tick-box. The individual is asked to rate their level of ability in five domains on a scale of 1 to 3, representing no problems (1), moderate problems (2) or severe problems (3) in each area: mobility; self-care; usual activities; pain/discomfort; and anxiety/depression. This allows 243 different health states to be defined via a five-digit descriptive rating of the five domains, from 11111, representing no problems in any domain, to 33333, severe problems in all domains. It is important to note that these scores are descriptive only and do not have any arithmetic properties. The second page asks the participant to rate how good or bad they feel their health is on a visual analogue scale from 0 (worst imaginable health state) to 100 (best imaginable

health state). This gives a percentage score which can be used as a quantitative measure of the individual's health at a given point in time.

8.1.7.3.2 RAND-36

The RAND-36 questionnaire is a widely-used, standardised measure of health-related quality of life (Hays et al. 1993; Hays & Morales 2001). Thirty-six multiple-choice items assess physical, mental and social functioning over eight domains: physical functioning; role limitation related to health problems; role limitation related to emotional problems; social functioning; emotional wellbeing; energy/fatigue; pain; and general health perceptions. Each item has between 2 and 6 possible answers, answered by tick-box, with each answer allocated a value between 0 and 100. Questions are grouped together into domains, and the values for each question are added together to give a percentage score for each domain. An overall total percentage is also calculated. Repeated measures give an indication of change in status in each domain over time.

8.1.7.3.3 pESS

A review of the properties and utility of the pESS is included in Chapter 5.

8.1.7.3.4 Healthcare usage

Information on frequency of use of healthcare services over the preceding month, including GP, nurse and hospital visits and planned and unplanned hospital admissions, was collected via a simple checklist.

8.1.7.3.5 Caffeine and medication use

Participants were asked to report their average daily intake of tea, coffee and caffeinated soft drinks over the preceding month, by the number of drinks. Current prescribed and unprescribed medications were listed in a free-text box, which were coded by the investigators using the ATC-DDD classification (see Chapter 5).

8.1.7.3.6 Relative/carer questionnaires

At baseline, 1 month, 3 months, 6 months and 12 months, relative/carers were asked to complete questionnaires including:

- Developmental Behaviour Checklist for Adults (DBC-A)

- Modified Zarit Burden Inventory (ZBI)
- General Health Questionnaire (GHQ-12)
- Epworth Sleepiness Scale (ESS) - giving their rating of the participant's sleepiness

These questionnaires were completed by the same carer/relative at all visits as far as possible to allow direct comparison of scores and outcomes and minimise inter-rater variability. In the event of a different carer/relative attending, the questionnaire was sent to the usual carer to complete and return, by either post of email.

8.1.7.3.7 DBC-A

A review of the properties and utility of the DBC-A is provided in Chapter 5.

8.1.7.3.8 Modified ZBI

The impact of caring for the individual with DS on their relative/carer was assessed using the short version of the Zarit Burden Interview (ZBI; Bédard et al. 2001). This 12-item questionnaire is a modified version of the original ZBI, which was developed to assess the level of burden experienced by caregivers of individuals with Alzheimer's disease (Zarit et al. 1985). The short version has been shown to give comparable results to the full version (Bédard et al. 2001), and was selected for use in this study to reduce the time constraint on the participant's relative/carer. The individual is asked to rate 12 statements about their experience of caring on a Likert-type scale of 0-4, where 0=never, 1=rarely, 2=sometimes, 3=quite frequently and 4=nearly always. The scores for all 12 questions are totalled together to give a score in the range 0-48 (Bédard et al. 2001).

8.1.7.3.9 GHQ-12

the General Health Questionnaire (GHQ) is a 60-item, self-rated questionnaire, originally designed to detect psychiatric illness in a community setting (Goldberg 1972). For simplicity and expediency of questionnaire completion, the shorter 12-item version (GHQ-12) was used (Goldberg & Williams 1988); reliability and validity of both versions are comparable. Twelve questions relating to mental health and wellbeing of the individual (in this case, the relative or carer of the adult with

DS) are presented with 4 possible answers. These can be scored in a number of ways; in this study, we opted to use the Likert scoring method, in which answers are coded 0-4 and the 12 answers summed to give a score in the range 0-36, with higher scores indicating a higher level of psychiatric burden (Goldberg & Williams 1988).

8.1.7.3.10 pESS

The pESS was used, as per the patient questionnaire. However, on this occasion, it was used as a proxy measure, with the relative/carer rating the participant's sleepiness. The use of the ESS/pESS as a proxy measure is discussed in Chapter 5.

8.1.7.4 GP information

A standard letter (see Appendix 3) was sent to each participant's general practitioner to inform them of the individual's participation in the study. Copies of the participant and carer information sheets were included, along with a copy of the signed consent form. Letters were sent to any other health professionals actively involved with the participant's care at the time of the study, such as hospital specialists, nurse practitioners or care workers.

8.1.7.5 Discussion of sleep study results

Time was taken to discuss the results of the participant's home sleep study with the participant and their relative/carer. In particular, the significance of the AH and ODI were highlighted, along with any suggested relationship to position or probable sleep stage. This provided an opportunity for the family to ask questions regarding the participant's diagnosis, improving their understanding of the need for treatment and the possible benefits prior to randomisation.

8.1.7.6 Randomisation

After completion of all anthropometric measures, cognitive function tests and questionnaires, participants were randomly allocated to either the treatment group or lifestyle group.

Randomisation was by balanced block design (Altman & Bland 1999). Blocks were created by an investigator not chiefly involved in either testing or treatment, and individual allocations placed in sealed, numbered envelopes.

Randomisation envelopes were opened sequentially at the time of randomisation by an unblinded investigator. Upon randomisation, patients were allocated individual, sequential identification numbers, from DSR01-DSR28 (with DSR an acronym for Down syndrome randomised). These numbers were used for identification of participants throughout the study and allowed anonymised storage of data. The randomisation envelope and allocation slip was filed in the unblinded CRF.

The unblinded investigator explained the allocation to the participant and their relative/carer, and issued a participant folder (see Appendix 3). This included: a "People You Will Meet" sheet with photos of the study team and contact details; copies of the participant and carer information sheets; a copy of the signed consent form; a lifestyle advice information sheet; 12 diary questionnaires to be completed and returned to the unblinded investigator in a pre-paid envelope on a monthly basis, commencing from one month after the baseline visit; and a list of all study appointment dates. Participants and relative/carers were advised to use the unblinded investigator as the primary point of contact with all study-related queries from this point forward so as to maintain the other investigators' blinding to treatment status.

8.1.8 Follow-up: 1 week (Visit 3)

Participants on both limbs of the study were followed up by telephone consultation with an unblinded investigator at 1 week. Any CPAP adherence issues were dealt with and further troubleshooting appointments, in person or by phone, were offered if required.

8.1.9 Follow-up: 1 month (Visit 4)

Participants in both limbs of the study attended for follow-up at 1 month from baseline. Cognitive function tests and questionnaires were completed as at baseline.

At the end of this visit, participants in the lifestyle limb were offered CPAP. Those accepting were initiated on CPAP via the same procedure as those commencing CPAP at baseline (see Figure 23 above and Section 8.1.14 below).

8.1.10 Follow-up: 1 month + 1 week (Visit 4a and 4b)

Participants randomised to the lifestyle group who commenced CPAP at the end of 1 month were followed up in the same manner as those randomised to the CPAP group A phone follow-up was completed after one week (visit 4a, procedure as visit 3 above) and one month (visit 4b, procedure as visit 4 above). This model allowed assessment of treatment effects to be made within the lifestyle group (i.e. before commencing CPAP versus after one month on CPAP), as well as between groups after one month (i.e. CPAP group versus lifestyle group).

All test procedures at visits 4 and 4b were carried out by a second blinded investigator to prevent unblinding of the main blinded investigator whilst minimising inter-rater variability.

8.1.11 Follow-up: 3, 6 and 12 months (Visits 5, 6 and 7)

All participants attended for follow-up at 3, 6 and 12 months from baseline. Cognitive function tests and questionnaires were completed as at baseline by blinded investigator.

8.1.12 Monthly diary

Participants and relative/carers were asked to complete a monthly diary questionnaire throughout the 12 month period (see Appendix 3). This recorded GP and hospital visits, caffeine intake, medication and CPAP side effects. Participants completed the ESS and EQ-5D. Relative/carers completed the pESS (as a proxy measure, rating the participant's sleepiness) and modified DBC-A, as well as providing qualitative feedback on their relative's progress. Diary questionnaires were returned by pre-paid envelope to the unblinded investigator and filed in the unblinded CRF.

8.1.13 Lifestyle advice

Participants in both arms of the study received a lifestyle advice package, written using easy-read format and pictorial information (see Appendix 3). The information package was discussed with participants and relative/carers by the unblinded investigator after randomisation at the end of the baseline visit. Each family was

advised to read through the information at home in their own time and to contact the unblinded investigator with any questions.

Information contained in the package was based on standard sleep hygiene advice issued to clinical patients attending the Department of Sleep Medicine. Guidance was given regarding the sleeping environment, including controlling light and temperature and avoiding electronic devices such as televisions, computers and mobile phones which may disrupt circadian rhythm. Participants were advised to avoid exercise, caffeine, tobacco and nicotine close to bedtime. The importance of daylight exposure, strengthening circadian rhythm, was highlighted, and participants were recommended to initiate a good bedtime routine. Specific advice regarding the non-therapeutic management of snoring and daytime sleepiness was provided.

8.1.14 Initiation and monitoring of CPAP

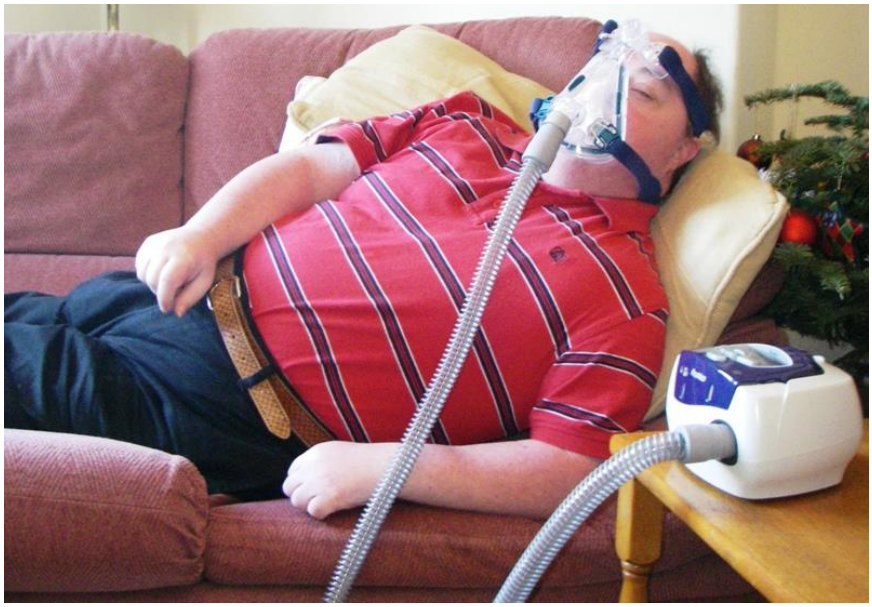
The literature shows that adherence to CPAP and subsequent therapeutic outcomes can be improved by intensive CPAP education and support (Hoy et al. 1999; Engleman & Wild 2003). CPAP therapy was initiated and monitored by an unblinded investigator with eight years' experience in administering CPAP therapy, in line with international recommendations (Morgenthaler et al. 2008).

8.1.15 CPAP device

All participants receiving CPAP were issued with an auto-titrating CPAP device (S8 AutoSet Spirit II™; ResMed (UK) Ltd., Abingdon, UK) with standard 2m hose and removable secure digital (SD) data card for recording of usage data (ResMed Ltd 2008) – see Figure 29. Autosetting CPAP machines by ResMed and other manufacturers are used widely worldwide and have been well validated (Farré et al. 2002; Senn et al. 2003; Cross et al. 2006; Sériès et al. 2008; McArdle et al. 2010; Vennelle et al. 2010).

CPAP units were set up and data downloaded and reported via a PC running specialised software (ResScan™ version 03.11.009, ResMed (UK) Ltd., Abingdon, UK).

Figure 29: ResMed S8 AutoSet Spirit II™ CPAP machine with hose and Mirage Quattro™ full face mask.



8.1.15.1 Pressure

All CPAP devices were initially set to variable pressure mode, with pressure ranges set to the default minimum of 4cmH_2O and maximum of 20 cmH_2O. However, the unblinded investigator could, optionally, curtail or fix pressures as required at any point in the study, depending on the participant's individual requirements and the unblinded investigator's clinical experience and judgement. Median, 95th centile and maximum pressure (all cmH_2O) were reported.

The CPAP units offer an expiratory pressure relief feature (EPR), which senses expiration and reduces the delivered CPAP pressure by 1, 2 or 3cmH_2O (ResMed Ltd 2008); this is a comfort feature which may be of particular benefit to individuals requiring very high CPAP pressures, who may experience difficulty breathing out against the pressure, resulting in an increased frequency of awakening at higher pressures. The EPR function was initially switched off and locked, but was altered by the investigator as required during troubleshooting.

The ramp or settling time was set to a default of 30min; this is the duration of the interval between the airflow switching on and treatment commencing, during which time the machine runs continually at minimum pressure. It is a comfort feature, allowing users a period in which they can settle and fall asleep before pressure variation begins. Ramp time was locked so participants could not alter it themselves. However, the unblinded investigator could adjust the ramp time as required during troubleshooting.

The SmartStart™ facility, which allows the machine to run and record data only when it senses that the mask is in contact with the patient's face - thereby avoiding falsely elevated compliance - was switched on in all cases and could not be altered by the participant.

8.1.15.2 Leak

Mask leak was recorded and reported in l/sec, with a leak of <4.0l/sec considered acceptable; a certain amount of intentional leak is expected due to the mask exhalation port which allows exhaled air to be expelled, preventing a build-up of carbon dioxide within the mask. Increased mask leak has been linked to poor CPAP adherence (Valentin et al. 2011).

8.1.15.3 Breathing events

Breathing events, classified as hypopnoea, obstructive apnoea, central apnoea or unknown apnoea, were detected and recorded, and used to create an AHI based on the hours of CPAP use per night. Events were classified as "unknown" in the event of high mask leak, during which the open or closed status of the airway cannot be assessed accurately by the CPAP machine. An AHI of <5 is considered normal, as per SIGN guidelines (Scottish Intercollegiate Guidelines Network 2003).

8.1.15.4 Compliance/adherence

CPAP compliance (mean number of hours per night) was recorded using the inbuilt machine timeclock, which records periods for which the machine is on and being used, and provide the standard method for monitoring CPAP compliance (H. M. Engleman et al. 1994).

A range of usage variables were reported:

- Total number of calendar days on which CPAP was used (days).
- Total number of calendar days on which CPAP was used for ≥4hr - generally considered the therapeutic minimum (Weaver & Grunstein 2008) (days).
- Total number of calendar days on which CPAP was used for <4hr (days).
- Total number of calendar days on which CPAP was not used (days).
- Percentage of days on which CPAP was used for ≥4hr (%).
- Median daily usage (hr/day).
- Total hours used (hr).
- Mean daily usage (hr/day), calculated on total days in reporting period (i.e. days used + days not used).

Summary graphs of usage, pressure and leak were produced, providing a visual representation of these variables over the reporting period.

8.1.15.5 Humidification

Heated humidification was not issued at commencement of therapy as standard, but was available as an adjunct and was prescribed, as required, by the unblinded investigator using her clinical judgement using an integrated heated humidifier (HumidAire 3i™ or H4i™, ResMed (UK) Ltd., Abingdon, UK). Symptoms which indicate the addition of humidification include dryness of the nose/mouth, nasal congestion or sneezing (Martins de Araújo 2000; Koutsourelakis et al. 2010; Worsnop et al. 2010).

8.1.15.6 CPAP interfaces and hose

A range of styles, sizes and brands of mask were available, and participants had the opportunity to try a number of different masks during their education session to ensure best fit and comfort. Available masks are shown in Table 31. A standard 2m CPAP hose, provided as part of the CPAP machine, was used.

8.1.15.7 CPAP initiation

CPAP therapy was commenced at the end of visit 2 for participants randomised to the CPAP group and at the end of visit 4 for participants in the lifestyle group. CPAP

initiation was generally carried out on an individual basis but, similarly to home study education, group education was occasionally employed where groups of friends participating in the study attended together by choice. The education and mask fitting session was conducted in line with the usual clinical procedure followed within the Department.

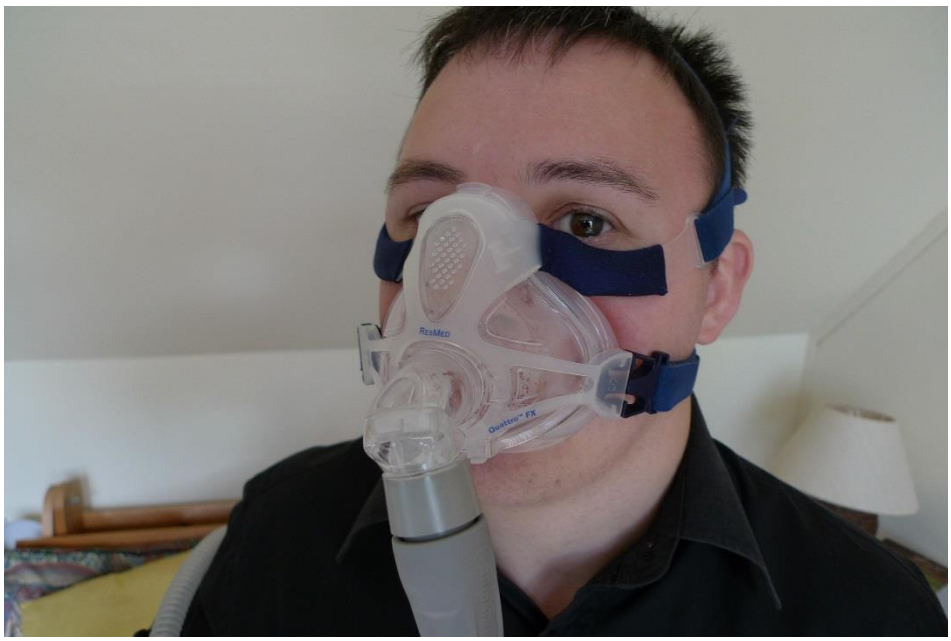
All participants and their relative/carers were shown an in-house instructional film as used in the Department for education of clinical patients. This discusses clinical features and consequences of obstructive sleep apnoea and describes CPAP treatment. Visual CPAP education has been shown to aid CPAP compliance in the general population (Basoglu et al. 2011), and, although the film was produced for the general, mainstream clinical population and, as such, does not use simplified language, the visual nature of the medium lends itself to people with DS, who tend to be visual learners (Hodapp & Dykens 2009). Since the film was produced in-house, it features staff and locations involved in the research study; this may help participants to directly relate the information on screen to their own situation, providing familiarity, which may in turn encourage better outcomes relating to CPAP therapy (Heller et al. 2006).

Following the video, each participant was fitted with a suitable CPAP mask from the range available by the unblinded investigator, an experienced CPAP nurse. The patient interface has been shown to be an important factor determining CPAP use (Parthasarathy 2008). Time was taken to desensitise the participant, allowing them to handle the mask themselves and explore it in their own time, including holding and fitting it to the face themselves, with and without the CPAP machine running. The participant and relative/carer were shown how to correctly fit and adjust the mask. Desensitisation protocols have been shown to be beneficial, improving compliance and adherence in a number of populations, including the general adult population (Engleman & Wild 2003).

Table 31: Range of CPAP interfaces available to study participants. Each participant had a suitable mask fitted from this range by an experienced CPAP nurse to ensure optimum fit and comfort.

Mask type	Manufacturer	Model	Sizes
Full face	ResMed (UK) Ltd., Abingdon, UK	Mirage Quattro™	Extra small, small
Full face	ResMed (UK) Ltd., Abingdon, UK	Quattro™ FX	Small
Full face	Philips Respironics, Chichester, UK	Amara	Petite

Figure 30: Study participant wearing ResMed Quattro™ FX full face mask.



Once the participant was fitted with a suitable mask and was comfortable enough to use it with the air pressure switched on, they were encouraged to lie down with the mask and machine on for a short period. During this time, the relative/carer could remain in the bedroom with the participant, and lights could be left on or switched off at the participant's preference. This allowed a short period of acclimatisation to the sensation of pressure flow, as well as offering the investigator an opportunity to assess and rectify unintentional mask leak, changing to a different style of mask if required. Upon leaving the room, the investigator monitored the participant remotely via infra-red video, and the participant or relative/carer could call the investigator for assistance using a patient buzzer system.

During the course of the study, the unblinded investigator attended training courses run by Down's Syndrome Scotland aimed at understanding and managing the behaviour of children and young people with Down's syndrome and improving compliance with medical treatments using behavioural techniques (Improving the Health and Well Being of Children and Adults with Learning Disabilities, 26 April 2013, Medica CPD; Positive Behaviour Support, 23 May 2013, Down's Syndrome Scotland). Skills gained by the unblinded investigator were incorporated into the CPAP initiation and support process to optimise treatment success.

8.1.15.8 CPAP follow-up and troubleshooting

Participants' adherence and response to CPAP therapy was monitored by the unblinded investigator, with steps taken to optimise these throughout. Participants and their relatives/carers were encouraged to report any problems by phone or email at any point during the study. All participant contact (face-to-face, phone or email), including time spent on each interaction, was documented in the unblinded CRF.

CPAP machines were downloaded at each visit. The unblinded investigator reviewed usage, compliance, leak and AHI over the study period and action was taken to optimise these outcomes at every stage. The optimal desired thresholds were: average usage ≥4hr/night; AHI <5; leak <0.4l/sec (Scottish Intercollegiate Guidelines Network 2003; Weaver & Grunstein 2008; Morgenthaler et al. 2008). Adverse events were recorded and rectified where possible. Mask fit was assessed subjectively by

the unblinded investigator, with the fit of the current mask optimised or a new mask issued. Humidification was prescribed as required (Engleman & Wild 2003).

8.1.16 Study completion

At the end of the 12 month follow-up visit, participants were encouraged to continue on CPAP therapy. Participants from within the catchment area of the Department of Sleep Medicine were integrated into the local clinical pathway and issued with a clinical CPAP unit. Participants from outwith the local area were referred to their nearest NHS sleep service. Formal referral letters were sent by a consultant from the Department of Sleep Medicine, with copies sent to the participant and their GP. All participants wishing to continue on CPAP at the end of the study retained the research CPAP machine. Machines were retrieved from participants wishing to cease CPAP. A card thanking the participant and their family for their participation in the study was sent by the investigators.

8.1.17 Statistical analysis

As previously stated in the Acknowledgements, statistical analysis was overseen by an experienced Trial Statistician, Dr Linda J. Williams, Centre for Population Health Sciences, The University of Edinburgh. Analysis was conducted by the Investigator under the guidance of the Trial Statistician.

Standard statistical analyses were conducted using SPSS Statistics version 19 (IBM). All analyses were two-tailed, with significance set at $p=0.001$ to allow for the effects of multiple testing, where the number of significant findings by chance increases with the number of comparisons run. A value of $p=0.001$ was considered a cautious, but sensible, threshold for significance, being less conservative than other methods of correcting for multiple testing, such as the Bonferroni correction (Feise 2002). All variables were checked for normality. Discrete variables were evaluated using the Chi-square test, and the Student's t-test was used to evaluate normally-distributed continuous variables. The Mann-Whitney-U test was used for non-normally distributed data. Results are presented as mean ± standard deviation for normal variables, as median(IQR) for non-normally distributed variables or as number and percentage.

Pearson's rank correlations were used to explore associations between continuous variables, with results shown as Pearson's r and p-value.

Discrete variables were evaluated using the Chi-square test and continuous variables using the Student's T-test. Pearson's and Spearman's rank correlations were used to explore the correlations between parametric and non-parametric variables respectively. The Mann-Whitney-U test was used for non-parametric variables. Regression analysis was undertaken to explore significant associations between variables, using binary logistic regression for categorical variables and generalized linear modelling for continuous variables. Results are presented as mean ± standard deviation for parametric variables or as a median with interquartile range (IQR 25-75%) for non-parametric data as appropriate, or as number and percentage.

Up to the 1 month visit, the study was analysed as a randomised, controlled trial of CPAP therapy versus conservative lifestyle measures.

At the end of the 1 month visit, individuals in the lifestyle group commenced CPAP. Thereafter, all study participants were pooled into a single group, and the study analysed as a prospective cohort study.

8.2 Results

Trial entry and completion information is summarised in Figure 31. Of the 134 participants with a valid home sleep study result, described in Chapter 7, 32 (24%) were ineligible for the treatment phase of the trial. Of these, 27 had a negative sleep study (AH<10), 3 had positive sleep studies but were asymptomatic, one had previously trialled CPAP therapy and one was unable to comply with the protocol. Seven individuals had an inconclusive sleep study which was not repeated, although, in clinical practice, a polysomnographic sleep study would be indicated.

Ninety-seven eligible adults with DS were invited to participate in the treatment study, of which 69 did not participate. The majority (n=67) were unable to participate due to a lack of funding available to complete the study caused by the delay in ethical approval. One participant declined to join the treatment phase of the trial and one did not respond when contacted to book an appointment.

Twenty-eight individuals (19 male; 9 female) were enrolled in the study and were randomised. Twenty-four adults with DS and OSAHS completed the full 12 month study, with 19 continuing with CPAP and 5 discontinuing treatment at the end of the study. One individual withdrew immediately prior to the 12 month visit due to an unexpected close family bereavement. Although withdrawn from the study, participant and relative/carer questionnaires were completed and the participant's CPAP machine was downloaded, although the 12 month visit was not conducted. In the event of participant withdrawal, the CPAP machine was retrieved and downloaded, allowing compliance data to be obtained up to the withdrawal date.

Of the 28 participants enrolled, 24 were judged to have capacity to consent for themselves. The remaining four participants were deemed to lack capacity to consent, and so consent was given on their behalf by their parent/carer. In all cases, the individual's parent/carer was present during the consenting process, and the decision as to whether an individual could consent for themself was made by the investigator, with additional guidance from the parent/carer. No significant differences were noted between individuals with and without capacity to consent in terms of anthropometric characteristics, sleepiness, behaviour, cognitive function, general health or pre-CPAP AHI (data not shown), other than a significantly higher mean PAL errors to success noted in AWI at baseline (9±4 v. 4±2; $p=0.001$) and 5 months (8±5 v. 4±3; $p<0.0001$).

8.2.1 Baseline characteristics

Anthropometric characteristics of the enrolled participants at baseline are summarised in Table 32. No significant gender differences were evident.

The majority of participants (71%) reported a trisomy 21 karyotype and 7% reported mosaic DS, although 21% reported that their karyotype was unknown or had never been tested. Participants displayed moderate (64%) to severe (36%) levels of ID. Eighty-nine percent of individuals lived at home with a parent or parents, with the remaining 11% living in supported accommodation.

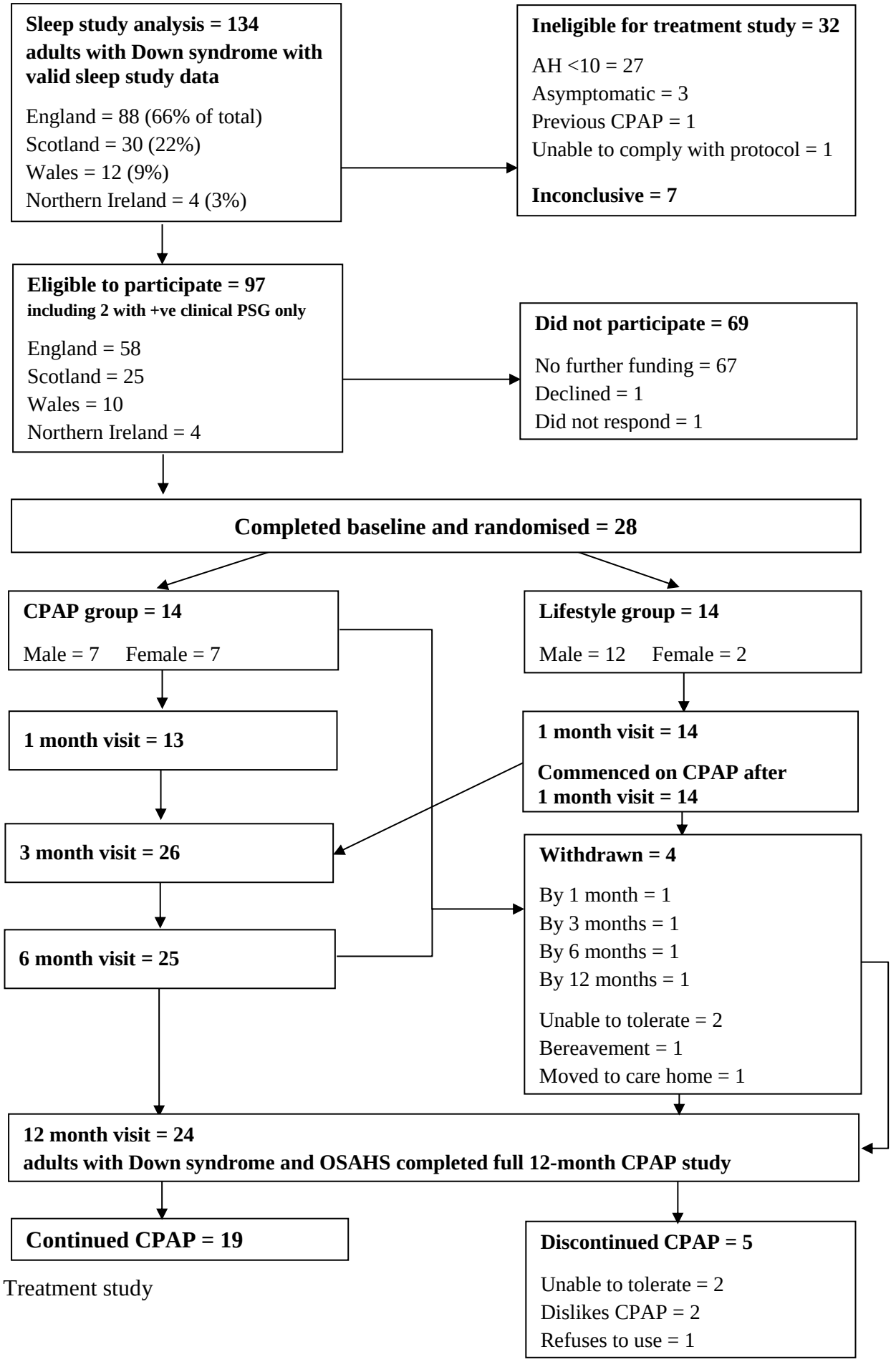
The mean age of participants was 28±9 years. Around a quarter of participants (26%) were of normal BMI, with the remainder in the overweight or obese category. The mean BMI was 31.5±7.9kg/m^2, with a trend towards a higher mean BMI in females (37.4±6.9kg/m^2; p=0.009).

8.2.1.1 Sleep characteristics

Subjective and objective sleep characteristics for all participants at study entry are detailed in Table 33Table 33: Subjective and objective sleep characteristics and subjective behaviour characteristics of participants enrolled in treatment study. Chi-square test used for parametric categorical variables, t-test for continuous categorical variables and Mann-Whitney U test for non-parametric variables. Values presented as mean±SD, median(IQR) or n% unless otherwise stated.. No significant gender differences were evident. The mean self-rated pESS was 11±6, with 41% exhibiting EDS (pESS>10). The mean pESS as reported by a relative or carer was 11±5, with 55% rated at having EDS.

The mean AH per hour in bed was 28.6(14.8-47.9), worse in the supine position (31.9(17.1-90.7)). The mean ODI was 7.3(1.8-21.9), again worse when supine (8.8(1.8-27.1)). A mean SpO2 of 93.8±3.5% was noted, falling to a nadir of 81.0±8.9%. A degree of flow limitation was evident, with a flattening index of 12.6(5.6-19.7). The mean heart rate was 60.1±8.1BPM, with a mean heart rate standard deviation of 6.3±1.9BPM, consistent with a degree of sleep fragmentation. On average, participants spent the majority of their sleep study (66(24-75)%) in the supine position, with a mean transition index of 2.0(1.0-4.1) position changes per hour in bed.

Figure 31: CONSORT diagram summarising enrolment in and completion of the treatment phase of the study.



Treatment study

Table 32: Anthropometric characteristics of participants enrolled in treatment study at baseline visit. Chi-square test used for parametric categorical variables and t-test for continuous categorical variables. Values presented as mean±SD or n%.

Characteristics	Total included	All participants n = 28		Male n = 19		Female n = 9		p *
Age (years)	28	28 ± 9		26 ± 8		31 ± 10		0.15
Body Mass Index (kg/m^2) **	27	31.5 ± 7.9		29.1 ± 7.0		37.4 ± 6.9		0.009
Underweight (<18.5kg/m^2)	27	0	0.0%	0	0.0%	0	0.0%	0.231
Normal weight (18.5-24.99kg/m^2)		7	25.9%	7	36.8%	0	0.0%	
Pre-obesity (25.0-29.99kg/m^2)		6	22.2%	4	21.1%	2	25.0%	
Obesity class I (30.0-34.99kg/m^2)		7	25.9%	5	26.3%	2	25.0%	
Obesity class II (35.0-39.99kg/m^2)		2	7.4%	1	5.3%	1	12.5%	
Obesity class III (≥40.00kg/m^2)		5	18.5%	2	10.5%	3	37.5%	
Collar size (cm)		41.5 ± 4.9		41.1 ± 3.9		42.3 ± 6.8		0.61
Form of DS:								
Trisomy 21	28	20	71.4%	15	78.9%	5	55.6%	0.48
Translocation		0	0.0%	0	0.0%	0	0.0%	
Mosaic		2	7.1%	1	5.3%	1	11.1%	
Unknown/not tested		6	21.4%	3	15.8%	3	33.3%	
Level of intellectual disability:								
Mild	28	0	0.0%	0	0.0%	0	0.0%	0.42
Moderate		18	64.3%	11	57.9%	7	77.8%	
Severe		10	35.7%	8	42.1%	2	22.2%	
Profound		0	0.0%	0	0.0%	0	0.0%	
Living arrangements:								
At home with parents	28	25	89.3%	18	94.7%	7	77.8%	0.23
Supported accommodation		3	10.7%	1	5.3%	2	22.2%	
Mallocclusion:								
A	28	5	17.9%	3	15.8%	2	22.2%	0.80
B		8	28.6%	5	26.3%	3	33.3%	
C		0	0.0%	0	0.0%	0	0.0%	
D		15	53.6%	11	57.9%	4	44.4%	
Macroglossia	28	9	32.1%	5	26.3%	4	44.4%	0.41
Gothic palate	28	26	92.9%	19	100.0%	7	77.8%	0.10
Adenoid facies	28	6	21.4%	3	15.8%	3	33.3%	0.35
Mallampati Score:								
Class I	28	1	3.6%	1	5.3%	0	0.0%	0.36
Class II		6	21.4%	5	26.3%	1	11.1%	
Class III		14	50.0%	10	52.6%	4	44.4%	
Class IV		7	25.0%	3	15.8%	4	44.4%	
Friedman Scale:								
Stage I	24	0	0.0%	0	0.0%	0	0.0%	0.63
Stage II		17	70.8%	11	64.7%	6	85.7%	
Stage III		7	29.2%	6	35.3%	1	14.3%	
Stage IV		0	0.0%	0	0.0%	0	0.0%	

Table 33: Subjective and objective sleep characteristics and subjective behaviour characteristics of participants enrolled in treatment study. Chi-square test used for parametric categorical variables, t-test for continuous categorical variables and Mann-Whitney U test for non-parametric variables. Values presented as mean±SD, median(IQR) or n% unless otherwise stated.

Sleep and behaviour characteristics	Total included	All participants n = 28	Male n = 19	Female n = 9	p *
Developmental Behaviour Checklist for Adults (DBC-A):					
Disruptive behaviour subscale (scale range 0-34)	28	4 (2-8)	4 (3-8)	4 (2-9)	0.77
Mean item score (possible score 0-2)	28	0.23 (0.13-0.47)	0.24 (0.18-0.47)	0.24 (0.12-0.53)	0.77
Proportion of items checked (possible score 0-1)	28	0.24 (0.13-0.47)	0.24 (0.18-0.47)	0.24 (0.12-0.50)	0.77
Intensity index (possible score 0-1)	27	0.00 (0.00-0.00)	0.00 (0.00-0.04)	0.00 (0.00-0.06)	1.00
Anxiety/Antisocial subscale (scale range -2-14)	28	0 (-1-1)	0 (-1-1)	0 (-1-1)	0.56
Mean item score (possible score 0-2)	28	0.00 (-0.11-0.11)	0.00 (-0.11-0.11)	0.00 (-0.06-0.06)	0.56
Proportion of items checked (possible score 0-1)	28	0.00 (0.00-0.11)	0.00 (0.00-0.11)	0.00 (-0.06-0.11)	0.56
Intensity index (possible score 0-1)	15	0.00 (0.00-0.50)	0.00 (0.00-0.88)	0.00 (0.00-0.00)	0.30
Depressive subscale (scale range 0-18)	28	1 (1-4)	1 (0-4)	2 (1-5)	0.47
Mean item score (possible score 0-2)	28	0.11 (0.11-0.44)	0.11 (0.00-0.44)	0.22 (0.11-0.50)	0.47
Proportion of items checked (possible score 0-1)	28	0.11 (0.11-0.44)	0.11 (0.00-0.44)	0.22 (0.11-0.44)	0.53
Intensity index (possible score 0-1)	22	0.00 (0.00-0.00)	0.00 (0.00-0.00)	0.00 (0.00-0.25)	0.57
Pictorial Epworth Sleepiness Scale (pESS):					
Self-rated	27	11 ± 6	11 ± 6	10 ± 6	0.82
Pictorial Epworth Sleepiness Scale score >10	27	11 40.7%	8 44.4%	3 33.3%	0.69
Carer-rated	20	11 ± 5	11 ± 5	12 ± 6	0.61
Pictorial Epworth Sleepiness Scale score >10	20	11 55.0%	7 53.8%	4 57.1%	1.00

Objective sleep study variables:					
Total recording time (min)	25	501.3 ± 104.7	518.8 ± 93.4	464.2 ± 123.9	0.23
Apnoeas/Hypopnoeas per hour in bed	24	28.6 (14.8-47.9)	26.8 (7.0-50.6)	30.0 (12.5-48.9)	1.00
Supine	24	31.9 (17.1-90.7)	31.9 (16.8-71.3)	35.1 (17.1-96.9)	0.83
Non-supine	24	20.0 (6.9-27.3)	20.0 (6.9-24.5)	18.6 (6.5-30.3)	0.79
Obstructive	24	3.6 (1.2-12.7)	3.9 (1.6-11.0)	1.6 (0.8-21.0)	0.49
Central	24	0.4 (0.0-1.2)	0.7 (0.1-1.6)	0.0 (0.0-0.5)	0.08
Mixed	24	0.0 (0.0-0.2)	0.0 (0.0-0.2)	0.0 (0.0-0.0)	0.32
Hypopnoea	24	22.3 (12.2-31.9)	22.3 (12.8-32.9)	21.1 (11.6-29.5)	0.79
Flattening index	6	12.6 (5.6-19.7)	10.2 ± 4.9	13.0 (4.6-30.5)	1.00
Mean SpO2 (%)	24	93.8 ± 3.5	94.3 ± 2.2	92.7 ± 5.6	0.48
SpO2 nadir (%)	24	81.0 ± 8.9	82.7 ± 5.7	77.0 ± 13.7	0.32
Average desaturation (%)	24	5.4 ± 1.2	5.0 ± 0.6	6.3 ± 1.8	0.10
Oxygen desaturation index per hour in bed	23	7.3 (1.8-21.9)	6.9 (3.0-18.3)	21.8 (0.7-43.5)	0.62
Supine	23	8.8 (1.8-27.1)	8.8 (2.8-24.1)	23.5 (1.1-44.2)	0.58
Non-supine	23	3.0 (0.6-19.4)	3.3 (1.3-8.2)	2.8 (0.0-32.9)	1.00
Mean heart rate (BPM)	23	60.1 ± 8.1	58.6 ± 8.0	63.7 ± 7.5	0.17
Mean standard devation of heart rate (BPM)	23	6.3 ± 1.9	6.7 ± 1.7	5.2 ± 2.2	0.08
Body position:					
Supine % of total recording time	25	65.7 (23.8-74.6)	69.0 (39.4-85.6)	40.4 (20.6-71.0)	0.14
Left % of total recording time	25	8.8 (0.0-21.5)	10.7 (0.0-28.8)	0.2 (0.0-11.7)	0.34
Prone % of total recording time	25	1.7 (0.0-15.5)	0.9 (0.0-9.1)	9.3 (0.3-41.4)	0.14
Right % of total recording time	25	13.9 (0.1-27.8)	11.4 (0.0-24.7)	26.7 (4.4-31.2)	0.09
Upright % of total recording time	25	0.1 (0.0-1.0)	0.0 (0.0-0.7)	0.7 (0.2-14.0)	0.049
Transition index per hour in bed	25	2.0 (1.0-4.1)	2.0 (0.5-3.6)	3.1 (1.7-5.4)	0.24

8.2.1.2 Behavioural and emotional disturbances

As summarised in Table 33, no significant gender differences were noted in terms of raw total scores, MIS, PIC or II on the DBC-A subscales at baseline.

8.2.2 Randomisation

Fourteen participants were randomly allocated to each group. As summarised in Tables 34, 35, 36 and 37. The groups were equivalent at baseline in terms of anthropometric characteristics, subjective and objective sleep characteristics, behavioural and emotional disturbances, cognitive function, general health status, medication use and carer burden at baseline, with no significant differences observed.

Although 86% of participants in each group used ≥1 medication, use of medications which may impact on sleep was very low, with one participant in the lifestyle group using an antiepileptic medication and one individual in the CPAP group taking antihistamines. As with the subjective and objective prevalence studies, category H drugs (systemic hormonal preparations excluding insulin) and category R (respiratory system) drugs were the most commonly used; 57% of the lifestyle group and 50% of the CPAP group used category H drugs (p=1.00), with category R medications used by 21% and 36% of the lifestyle and CPAP groups respectively (p=0.68).

Table 34: Anthropometric characteristics of participants enrolled in treatment study at baseline visit by randomisation group. Chi-square test used for parametric categorical variables and t-test for continuous categorical variables. Values presented as mean±SD or n %.

***Not yet commenced on CPAP**

Characteristics	**Total included**	**Lifestyle**		**CPAP ***		**p**
		n = 14		**n = 14**		
Gender (males : females)	28	12 : 2		7 : 7		0.10
Age (years)	28	27 ± 8		29 ± 10		0.54
Body Mass Index (kg/m^2)	27	30.0 ± 7.4		33.2 ± 8.3		0.29
Collar size (cm)	28	41.4 ± 4.2		41.6 ± 5.7		0.93
Form of DS:						
Trisomy 21	28	10	71.4%	10	71.4%	0.48
Translocation		0	0.0%	0	0.0%	
Mosaic		2	14.3%	0	0.0%	
Unknown/not tested		2	14.3%	4	28.6%	
Level of intellectual disability:						
Mild	28	0	0.0%	0	0.0%	0.70
Moderate		10	71.4%	8	57.1%	
Severe		4	28.6%	6	42.9%	
Profound		0	0.0%	0	0.0%	
Living arrangements:						
At home with parents	28	12	85.7%	13	92.9%	1.00
Supported accommodation		2	14.3%	1	7.1%	
Mallocclusion:						
A	28	2	14.3%	3	21.4%	0.88
B		4	28.6%	4	28.6%	
C		0	0.0%	0	0.0%	
D		8	57.1%	7	50.0%	
Macroglossia	28	4	28.6%	5	35.7%	1.00
Gothic palate	28	13	92.9%	13	92.9%	1.00
Adenoid facies	28	3	21.4%	3	21.4%	1.00
Mallampati Score:						
Class I	28	1	7.1%	0	0.0%	0.18
Class II		1	7.1%	5	35.7%	
Class III		7	50.0%	7	50.0%	
Class IV		5	35.7%	2	14.3%	
Friedman Scale:						
Stage I	24	0	0.0%	0	0.0%	0.07
Stage II		6	50.0%	11	91.7%	
Stage III		6	50.0%	1	8.3%	
Stage IV		0	0.0%	0	0.0%	

Table 35: Subjective and objective sleep characteristics and subjective behaviour characteristics of participants enrolled in treatment study by randomisation group. Chi-square test used for parametric categorical variables, t-test for continuous categorical variables and Mann-Whitney U test for non-parametric variables. Values presented as mean±SD, median(IQR) or n% unless otherwise stated.

***Not yet commenced on CPAP**

Sleep and behaviour characteristics	**Total included**	**Lifestyle n = 14**	**CPAP* n = 14**	**p**
Developmental Behaviour Checklist for Adults (DBC-A):				
Disruptive behaviour subscale (scale range 0-34)	28	5 (3-8)	4 (2-9)	0.84
Mean item score (possible score 0-2)	28	0.29 (0.16-0.47)	0.24 (0.10-0.50)	0.84
Proportion of items checked (possible score 0-1)	28	0.29 (0.16-0.47)	0.24 (0.10-0.49)	0.73
Intensity index (possible score 0-1)	28	0.00 (0.00-0.00)	0.00 (0.00-0.22)	0.43
Anxiety/Antisocial subscale (scale range -2-14)	28	1 (-1-1)	0 (0-1)	0.87
Mean item score (possible score 0-2)	28	0.06 (-0.11-0.11)	0.00 (-0.03-0.11)	0.87
Proportion of items checked (possible score 0-1)	28	0.06 (-0.03-0.13)	0.00 (-0.03-0.11)	0.67
Intensity index (possible score 0-1)	23	0.00 (0.00-0.25)	0.10 (0.00-1.00)	0.39
Depressive subscale (scale range 0-18)	28	2 (1-4)	1 (0-4)	0.73
Mean item score (possible score 0-2)	28	0.17 (0.11-0.44)	0.11 (0.00-0.47)	0.73
Proportion of items checked (possible score 0-1)	28	0.17 (0.11-0.44)	0.11 (0.00-0.39)	0.67
Intensity index (possible score 0-1)	22	0.00 (0.00-0.00)	0.00 (0.00-0.43)	0.25
Pictorial Epworth Sleepiness Scale (pESS):				
Self-rated	27	10 ± 5	11 ± 7	0.70
Pictorial Epworth Sleepiness Scale score >10	27	5 38.5%	6 42.9%	0.49
Carer-rated	20	10 ± 4	12 ± 6	0.36
Pictorial Epworth Sleepiness Scale score >10	20	5 50.0%	6 60.0%	0.53

Objective sleep study variables:				
Total recording time (min)	25	525.5 ± 102.6	475.2 ± 104.9	0.24
Apnoeas/Hypopnoeas per hour in bed	24	25.0 (15.8-46.5)	31.1 (14.1-50.1)	0.78
Supine	24	27.3 (17.2-46.4)	50.1 (16.9-97.3)	0.28
Non-supine	24	17.7 (6.0-24.3)	20.1 (7.4-36.8)	0.39
Obstructive	24	4.0 (1.1-9.9)	3.4 (1.2-23.7)	0.73
Central	24	0.2 (0.0-0.7)	3.9 (0.0-2.2)	0.277
Mixed	24	0.0 (0.0-0.2)	0.0 (0.0-0.0)	0.42
Hypopnoea	24	21.9 (11.9-30.5)	22.7 (12.2-33.0)	1.00
Mean SpO2 (%)	24	93.3 ± 4.2	94.4 ± 2.3	0.42
SpO2 nadir (%)	24	81.3 ± 8.9	80.7 ± 9.2	0.88
Average desaturation (%)	24	5.0 ± 0.8	6.0 ± 1.4	0.04
Oxygen desaturation index per hour in bed	23	7.5 (2.1-23.7)	7.3 (1.6-21.9)	1.00
Supine	23	7.9 (1.9-24.6)	9.8 (1.1-43.7)	0.61
Non-supine	23	3.3 (0.8-8.2)	2.8 (0.6-20.6)	0.83
Mean heart rate (BPM)	23	58.5 ± 8.9	62.0 ± 7.1	0.31
Mean standard devation of heart rate (BPM)	23	6.5 ± 1.8	6.0 ± 2.1	0.54
Body position:				
Supine % of total recording time	25	69.0 (46.7-85.6)	50.5 (20.4-74.0)	0.17
Left % of total recording time	25	8.8 (0.0-16.8)	5.5 (0.0-35.6)	0.81
Prone % of total recording time	25	0.4 (0.0-6.7)	4.7 (0.1-39.2)	0.186
Right % of total recording time	25	13.9 (6.2-29.6)	9.5 (0.0-27.2)	0.35
Upright % of total recording time	25	0.0 (0.0-0.5)	0.6 (0.0-1.7)	0.12
Transition index per hour in bed	25	2.0 (0.5-3.6)	2.5 (1.7-4.4)	0.38

Table 36: Cognitive function status of participants enrolled in treatment study by randomisation group at baseline visit. Chi-square test used for parametric categorical variables, t-test for continuous categorical variables and Mann-Whitney U test for non-parametric variables. Values presented as mean±SD, median(IQR) or n% unless otherwise stated.

***Not yet commenced on CPAP**

Cognitive function tests	**Total included**	**Lifestyle n = 14**	**CPAP * n = 14**	**p**
Kaufmann Brief Intelligence Test (KBIT-2):				
Raw score verbal	28	30.6 ± 17.6	31.9 ± 13.3	0.83
Raw score non-verbal	28	12.3 ± 6.3	14.4 ± 4.2	0.30
Scales of Independent Behaviour - Revised (SIB-R) Adaptive Behavior Short Form:				
Raw score	27	84.2 ± 14.6	80.1 ± 11.1	0.50
Modified DOTS task:				
Mean correct cats	-	-	-	-
Mean correct frogs	-	-	-	-
Mean correct combined	-	-	-	-
CANTAB Paired Associates Learning (PAL):				
Mean errors to success	27	4.5 ± 3.5	5.1 ± 2.9	0.62
First trial memory score	28	11.4 ± 7.4	9.9 ± 4.3	0.52
CANTAL Simple Reaction Time (SRT):				
Mean correct latency (ms)	28	606.8 ± 346.2	557.3 ± 311.8	0.69

Table 37: General health and carer burden status of participants enrolled in treatment study by randomisation group at baseline visit. Chi-square test used for parametric categorical variables, t-test for continuous categorical variables and Mann-Whitney U test for non-parametric variables. Values presented as mean±SD, median(IQR) or n % unless otherwise stated.

*** Not yet commenced CPAP therapy**

**** Includes oxygen**

Cognitive function tests	Total included	Lifestyle n = 14	CPAP * n = 14	p
EQ-5D:				
Mobility	28	0.0 (0.0-1.3)	0.0 (0.0-2.0)	0.60
Self-care	28	0.0 (0.0-1.3)	0.0 (0.0-1.3)	0.95
Usual activities	28	0.0 (0.0-2.0)	0.0 (0.0-1.3)	0.80
Pain/discomfort	28	1.0 (0.0-1.0)	0.0 (0.0-2.0)	0.84
Anxiety/depression	28	0.0 (0.0-1.0)	0.0 (0.0-1.0)	0.70
Health state (visual analogue scale; %)	27	80 (65-90)	93 (75-100)	0.08
RAND SF-36:				
Total percent	28	80.8 (63.2-85.0)	63.1 (40.1-81.7)	0.13
Physical functioning	27	90.0 (45.0-96.3)	65.0 (30.0-97.5)	0.26
Role limitations due to physical health	28	100.00 (100.0-100.0)	100.0 (18.8-100.0)	0.19
Role limitations due to emotional problems	28	100.0 (100.0-100.0)	100 (83.3-100.0)	0.73
Energy/fatigue	28	62.5 (48.8-65.0)	47.5 (32.5-55.0)	0.13
Emotional well-being	5	84.1 (76.2-84.1)	60.0 (32.0-60.0)	0.20
Social functioning	27	100.0 (71.9-100.0)	87.5 (68.8-100.0)	0.38
Pain	28	50.0 (49.4-90.0)	50.0 (40.6-80.0)	0.27
General health	28	80.0 (62.5-95.0)	75.0 (47.5-95.0)	0.76
General Health Questionnaire 12-item version (GHQ12):				
Total score	27	10.7 ± 2.5	10.5 ± 3.9	0.84
Modified carer burden inventory (CBI):				
Total score	27	10.8 ± 7.0	9.0 ± 6.7	0.51

Any medication	28	12	85.7%	12	85.7%	1.00
A - Alimentary tract and metabolism	28	5	35.7%	3	21.4%	0.68
B - Blood and blood forming organs	28	0	0.0%	1	7.1%	1.00
C - Cardiovascular system	28	1	7.1%	0	0.0%	1.00
D - Dermatologicals	28	1	7.1%	2	14.3%	1.00
G - Genito-urinary system and sex hormones	28	0	0.0%	1	7.1%	1.00
H - Systemic hormonal preparations, excluding sex hormones and insulins	28	8	57.1%	7	50.0%	1.00
J - Antiinfectives for systemic use	28	0	0.0%	1	7.1%	1.00
L - Antineoplastic and immunomodulating agents	28	0	0.0%	0	0.0%	-
M - Musculo-skeletal system	28	1	7.1%	1	7.1%	1.00
N - Nervous system	28	2	14.3%	0	0.0%	0.48
P - Antiparasitic products, insecticides and repellents	28	0	0.0%	0	0.0%	-
R - Respiratory system	28	3	21.4%	5	35.7%	0.68
S - Sensory organs	28	0	0.0%	0	0.0%	-
V - Various **	28	0	0.0%	0	0.0%	-
Over-the-counter medications with no clear WHO ATC category	28	0	0.0%	0	0.0%	-
Benzodiazepines	28	0	0.0%	0	0.0%	-
Antidepressants	28	0	0.0%	0	0.0%	-
Opiates	28	0	0.0%	0	0.0%	-
Oxygen	28	0	0.0%	0	0.0%	-
Melatonin	28	0	0.0%	0	0.0%	-
Antiepileptics	28	1	7.1%	0	0.0%	1.00
Contraceptives	28	0	0.0%	1	7.1%	1.00
Antihistamines	28	1	7.1%	1	7.1%	1.00

8.2.3 1 month follow-up

At this point, the study was analysed as a randomised, controlled trial of CPAP therapy versus conservative lifestyle measures.

When the randomised groups were compared at 1 month from baseline (Table 38), no significant differences were observed, despite the use of CPAP by one group. The CPAP group averaged 36±9 days from CPAP initiation at the time of the 1 month follow-up visit. CPAP had been used on 69.4(22.6-84.8)% of days since initiation, with 35.7(0.0-52.6)% of used days averaging ≥4hr usage, considered the conventional therapeutic minimum in the general population (Weaver & Grunstein 2008). Total usage averaged 62.4(13.0-110.3)hr, with a median usage of 3.0(1.6-4.7)hr/night. The mean 95^{th} centile pressure was 8.9±2.8cmH_2O, with a mean leak within normal limits (0.3(0.2-0.4)l/sec). The machine-derived AHI was 10.4(1.5-12.4) events/hr, with an AHI <5 per/hr considered the upper limit of normal. Pressure, leak and AHI data were unavailable for 1 participant due to a machine error. No significant differences were noted between those who consented for themselves and those who did not (data not shown).

8.2.4 Prospective treatment study

The lifestyle group did not differ significantly in outcomes between their baseline and 1 month visits (Table 39), both pre-CPAP, indicating that an additional pre-treatment visit did not have a significant effect in this group. Therefore, the lifestyle group baseline measures were pooled with the CPAP group baseline measures for use in the whole group prospective treatment study analysis.

Measured sleep, behaviour, cognitive function and general health outcomes for the whole group on CPAP across the 12 month study period are summarised in Table 40 (raw values at baseline, 3 months and 12 months) and Table 41 (change (Δ) values at 1, 3, 6 and 12 months). Again, no significant differences were noted between those who consented for themselves and those who did not (data not shown).

Table 38: Characteristics of lifestyle and CPAP groups at 1 month. Chi-square test used for parametric categorical variables, t-test for continuous categorical variables and Mann-Whitney U test for non-parametric variables. Values presented as mean±SD, median(IQR) or n % unless otherwise stated.

*** Not on CPAP**

**** No CPAP data for 1 participant due to machine error**

Characteristics	Total included	Lifestyle * n = 14	CPAP **	p
Body Mass Index (kg/m^2)	25	29.4 ± 7.0	34.1 ± 8.5	0.14
Collar size (cm)	26	41.1 ± 3.4	42.4 ± 6.8	0.53
Developmental Behaviour Checklist for Adults (DBC-A):				
Disruptive behaviour subscale (scale range 0-34)	26	4 (3-7)	3 (1-6)	0.84
Mean item score (possible score 0-2)	26	0.24 (0.15-0.41)	0.18 (0.06-0.32)	0.39
Proportion of items checked (possible score 0-1)	26	0.24 (0.15-0.38)	0.18 (0.06-0.32)	0.39
Intensity index (possible score 0-1)	25	0.00 (0.00-0.00)	0.00 (0.00-0.00)	0.81
Anxiety/Antisocial subscale (scale range -2-14)	26	0.0 (-1-1.0)	0 (-1-1)	0.34
Mean item score (possible score 0-2)	26	0.00 (-0.06-0.11)	0.00 (-0.11-0.11)	0.34
Proportion of items checked (possible score 0-1)	26	0.00 (-0.06-0.11)	0.00 (-0.11-0.11)	0.29
Intensity index (possible score 0-1)	18	0.00 (0.00-0.38)	0.00 (0.00-0.00)	0.63
Depressive subscale (scale range 0-18)	26	1 (1-2)	1 (0-3)	0.55
Mean item score (possible score 0-2)	26	0.11 (0.11-0.22)	0.11 (0.11-0.28)	0.55
Proportion of items checked (possible score 0-1)	26	0.11 (0.11-0.22)	0.11 (0.00-0.28)	0.51
Intensity index (possible score 0-1)	20	0.00 (0.00-0.00)	0.00 (0.00-0.00)	0.71
Pictorial Epworth Sleepiness Scale (pESS):				
Self-rated	26	9 ± 5	10 ± 6	0.70
Pictorial Epworth Sleepiness Scale score >10	26	4 30.8%	6 46.2%	0.69
Carer-rated	22	11 ± 4	11 ± 6	0.99
Pictorial Epworth Sleepiness Scale score >10	22	5 45.5%	6 54.5%	1.00
Arizona Cognitive Test Battery (ACTB):				
Kaufmann Brief Intelligence Test (KBIT-2):				
Raw score verbal	25	36.4 ± 18.1	35.9 ± 11.4	0.94
Raw score non-verbal	26	14.0 (12.5-17.5)	16.0 (11.58-17.0)	0.96
Scales of Independent Behaviour - Revised (SIB-R) Adaptive Behavior Short Form:				
Raw score	26	83.3 ± 15.4	82.2 ± 11.4	0.83
Modified DOTS task:				
Mean correct cats	25	0.38 ± 0.13	0.49 ± 0.13	0.04
Mean correct frogs	25	0.40 ± 0.13	0.42 ± 0.11	0.67
Mean correct combined	25	0.40 ± 0.12	0.43 ± 0.06	0.40
CANTAB Paired Associates Learning (PAL):				
Mean errors to success	26	2.0 (1.3-6.8)	3.0 (1.5-4.3)	0.80
First trial memory score	26	13.2 ± 6.1	12.4 ± 6.3	0.73
CANTAL Simple Reaction Time (SRT):				
Mean correct latency (ms)	26	576.1 ± 197.7	554.0 ± 280.4	0.82

General health measures:				
EQ-5D:				
Mobility	26	0.0 (0.0-1.0)	0.0 (0.0-1.5)	0.42
Self-care	26	0.0 (0.0-1.0)	0.0 (0.0-1.5)	0.76
Usual activities	26	0.0 (0.0-1.0)	1.0 (0.0-1.0)	0.88
Pain/discomfort	26	0.0 (0.0-0.5)	0.0 (0.0-2.0)	0.39
Anxiety/depression	26	0.0 (0.0-0.5)	0.0 (0.0-0.0)	0.84
Health state (visual analogue scale; %)	26	90.0 (77.5-98.5)	95.0-57.5-97.0)	0.69
RAND SF-36:				
Total (%)	26	75.6 (60.0-87.6)	69.2 (49.7-83.3)	0.29
Physical functioning (%)	25	92.5 (51.3-100.0)	75.0 (33.8-97.5)	0.27
Role limitations due to physical health (%)	24	100.0 (37.5-100.0)	100.0 (100.0-100.0)	0.94
Role limitations due to emotional problems (%)	26	100.0 (100.0-100.0)	100.0 (100.0-100.0)	0.58
Energy/fatigue (%)	26	65.0 (47.5-75.0)	50.0 (27.5-67.5)	0.17
Emotional well-being (%)	5	80.1 (76.2-80.1)	72.0 (64.0-72.0)	0.20
Social functioning (%)	26	87.5 (62.5-100.0)	100.0 (100.0-100.0)	0.31
Pain (%)	26	50.0 (50.0-77.5)	50.0 (47.5-90.0)	0.92
General health (%)	26	80.0 (72.5-95.0)	85.0 (60.0-97.5)	0.84
Carer-related measures:				
General Health Questionnaire 12-item version (GHQ12):				
Total score	24	11.2 ± 3.5	9.6 ± 4.4	0.32
Modified carer burden inventory (CBI):				
Total score	25	12.8 ± 7.7	8.9 ± 8.4	0.24
Continuous positive airway pressure (CPAP) :				
Total days since CPAP initiation	13	-	36 ± 9	-
Days used (%)	13	-	69.4 (22.6-84.8)	-
Days used ≥4hr (%)	13	-	35.7 (0.0-52.6)	-
Total usage (hr)	13	-	62.4 (13.0-110.3)	-
Mean usage (hr)	13	-	1.9 (0.2-4.0)	-
Median usage (hr)	13	-	3.0 (1.6-4.7)	-
95th centile pressure (cmH_20)	12 **	-	8.9 ± 2.8	-
95th centile leak (L/min)	13 **	-	0.3 (0.2-0.4)	-
Apnoea/hypopnoea index (derived from CPAP machine)	14 **	-	10.4 (1.5-12.4)	-

Table 39: Characteristics of participants in the lifestyle group at baseline and 1 month (not on CPAP). Chi-square test used for parametric categorical variables, t-test for continuous categorical variables and Mann-Whitney U test for non-parametric variables. Values presented as mean±SD, median(IQR) or n % unless otherwise stated.

Characteristics	Total included	Baseline n = 14	1 month n = 13	p
Body Mass Index (kg/m^2)	27	30.0 ± 7.4	29.4 ± 7.0	0.83
Collar size (cm)	27	41.4 ± 4.2	41.0 ± 3.4	0.82
Developmental Behaviour Checklist for Adults (DBC-A):				
Disruptive behaviour subscale (scale range 0-34)	27	5 (3-8)	4 (3-7)	0.55
Mean item score (possible score 0-2)	27	0.32 (0.16-0.47)	0.24 (0.15-0.41)	0.55
Proportion of items checked (possible score 0-1)	27	0.29 (0.16-0.47)	0.24 (0.15-0.38)	0.52
Intensity index (possible score 0-1)	27	0.00 (0.00-0.00)	0.00 (0.00-0.00)	0.98
Anxiety/Antisocial subscale (scale range -2-14)	27	1 (-1-1)	0 (-1-1)	1.00
Mean item score (possible score 0-2)	27	0.06 (-0.11-0.11)	0.00 (0.00-0.11)	1.00
Proportion of items checked (possible score 0-1)	27	0.06 (-0.03-0.14)	0.00 (-0.06-0.11)	0.72
Intensity index (possible score 0-1)	17	0.00 (0.00-0.25)	0.00 (0.00-0.38)	1.00
Depressive subscale (scale range 0-18)	27	2 (1-4)	1 (1-2)	0.58
Mean item score (possible score 0-2)	27	0.17 (0.11-0.44)	0.11 (0.11-0.22)	0.58
Proportion of items checked (possible score 0-1)	27	0.17 (0.11-0.44)	0.11 (0.11-0.22)	0.58
Intensity index (possible score 0-1)	23	0.00 (0.00-0.00)	0.00 (0.00-0.00)	1.00
Pictorial Epworth Sleepiness Scale (pESS):				
Self-rated	26	10 ± 5	9 ± 5	0.59
Pictorial Epworth Sleepiness Scale score >10	26	5 38.5%	4 30.8%	1.00
Carer-rated	21	10 ± 4	11 ± 4	0.82
Pictorial Epworth Sleepiness Scale score >10	21	5 50.0%	5 45.5%	1.00
Arizona Cognitive Test Battery (ACTB):				
Kaufmann Brief Intelligence Test (KBIT-2):				
Raw score verbal	26	30.6 ± 17.6	36.4 ± 18.1	0.42
Raw score non-verbal	27	12.3 ± 6.3	21.9 ± 20.3	0.13
Scales of Independent Behaviour - Revised (SIB-R) Adaptive Behavior Short Form:				
Raw score	27	84.2 ± 14.6	83.3 ± 15.4	0.88
Modified DOTS task:				
Mean correct cats	12	-	0.38 ± 0.13	-
Mean correct frogs	12	-	0.40 ± 0.13	-
Mean correct combined	12	-	0.40 ± 0.12	-
CANTAB Paired Associates Learning (PAL):				
Mean errors to success	26	3.0 (1.9-6.4)	2.0 (1.3-6.8)	0.34
First trial memory score	27	11.4 ± 7.4	13.2 ± 6.1	0.48
CANTAL Simple Reaction Time (SRT):				
Mean correct latency (ms)	27	530.0 (338.3-772.6)	624.6 (358.9-703.9)	0.69

General health measures:				
EQ-5D:				
Mobility	27	0.0 (0.0-1.3)	0.0 (0.0-1.0)	0.72
Self-care	27	0.0 (0.0-1.3)	0.0 (0.0-1.0)	0.91
Usual activities	27	0.0 (0.0-2.0)	0.0 (0.0-1.0)	0.91
Pain/discomfort	27	1.0 (0.0-1.0)	0.0 (0.0-0.5)	0.16
Anxiety/depression	27	0.0 (0.0-1.0)	0.0 (0.0-0.5)	0.58
Health state (visual analogue scale; %)	27	80.0 (65.0-90.0)	90.0 (77.5-98.5)	0.14
RAND SF-36:				
Total (%)	27	80.8 (63.2-85.0)	75.6 (60.0-87.6)	0.91
Physical functioning (%)	27	90.0 (45.0-96.3)	92.5 (51.3-100.0)	0.56
Role limitations due to physical health (%)	27	100.0 (100.0-100.0)	100.0 (100.0-100.0)	0.49
Role limitations due to emotional problems (%)	27	100.0 (100.0-100.0)	100.0 (100.0-100.0)	0.79
Energy/fatigue (%)	27	62.5 (48.8-65.0)	65.0 (47.5-75.0)	0.62
Emotional well-being (%)	4	84.1 (76.2-84.1)	80.1 (76.2-80.1)	0.67
Social functioning (%)	27	100.0 (100.0-100.0)	87.5 (62.5-100.0)	0.49
Pain (%)	27	50.0 (49.4-90.0)	50.0 (50.0-77.5)	0.58
General health (%)	27	80.0 (62.5-95.0)	80.0 (72.5-95.0)	0.98
Carer-related measures:				
General Health Questionnaire 12-item version (GHQ12):				
Total score	27	10.7 ± 2.5	11.2 ± 3.5	0.66
Modified carer burden inventory (CBI):				
Total score	27	10.8 ± 7.0	12.8 ± 8	0.49

Table 40: Measured outcomes in all participants at baseline, 3 month and 12 month visits. Paired samples t-test used for parametric variables and Wilcoxon ranked pairs test for non-parametric variables. Values presented as mean±SD or median(IQR).

*** Comparison of baseline & 3 month visits**

**** Comparison of baseline & 12 month visits**

***** Comparison of 3 month & 12 month visits**

	Baseline visit		3 month visit			12 month visit		
	n = 28		n = 26			n = 24		
Participant characteristics	**Total included**	**Value**	**Total included**	**Value**	**p ***	**Total included**	**Value**	**p ****
Body Mass Index (kg/m^2)	26	31.0 ± 7.5	24	31.9 ± 7.5	0.02	23	32.5 ± 7.3	0.16
Collar size (cm)	27	41.3 ± 4.9	25	41.7 ± 5.1	0.50	24	41.7 ± 5.3	1.00
Developmental Behaviour Checklist for Adults (DBC-A):								
Disruptive behaviour subscale (scale range 0-34)	28	4 (2-8)	26	2 (1-5)	0.002	23	1 (0-3)	<0.0001
Mean item score (possible score 0-2)	28	0.24 (0.13-0.47)	26	0.12 (0.06-0.31)	0.002	23	0.06 (0.00-0.18)	<0.0001
Proportion of items checked (possible score 0-1)	28	0.24 (0.13-0.47)	26	0.12 (0.06-0.25)	0.001	23	0.06 (0.00-0.18)	<0.0001
Intensity index (possible score 0-1)	27	0.00 (0.00-0.00)	22	0.00 (0.00-0.00)	0.25	17	0.00 (0.00-0.00)	0.29
Anxiety/Antisocial subscale (scale range -2-14)	28	0 (-1-1)	26	0 (-1-1)	0.05	23	0 (-1-0)	0.03
Mean item score (possible score 0-2)	28	0.00 (-0.11-0.11)	26	0.00 (-0.11-0.11)	0.05	23	0.00 (-0.11-0.00)	0.03
Proportion of items checked (possible score 0-1)	28	0.00 (0.00-0.11)	26	0.00 (-0.11-0.11)	0.06	23	0.00 (-0.11-0.00)	0.02
Intensity index (possible score 0-1)	15	0.00 (0.00-0.50)	13	0.00 (0.00-0.75)	0.32	8	0.00 (0.00-0.75)	1.00
Depressive subscale (scale range 0-18)	28	1 (1-4)	26	1 (0-2)	0.01	23	0 (0-1)	0.001
Mean item score (possible score 0-2)	28	0.11 (0.11-0.44)	26	0.06 (0.00-0.17)	0.01	23	0.00 (0.00-0.11)	0.001
Proportion of items checked (possible score 0-1)	28	0.11 (0.11-0.44)	26	0.06 (0.00-0.17)	0.01	23	0.00 (0.00-0.11)	0.001
Intensity index (possible score 0-1)	22	0.00 (0.00-0.00)	13	0.00 (0.00-0.00)	0.20	7	0.00 (0.00-0.00)	1.00
Pictorial Epworth Sleepiness Scale (pESS):								
Self-rated	27	11 ± 6	25	7 ± 6	<0.0001	24	6 ± 5	0.001
Carer-rated	20	11 ± 5	19	9 ± 5	0.02	16	7 ± 5	0.03

Arizona Cognitive Test Battery (ACTB):								
Kaufmann Brief Intelligence Test (KBIT-2):								
Raw score verbal	28	31.3 ± 15.3	26	31.6 ± 15.6	0.002	24	37.4 ± 18.6	0.001
Raw score non-verbal	28	13.4 ± 5.4	26	18.1 ± 13.0	0.05	24	19.5 ± 17.1	0.01
Scales of Independent Behaviour - Revised (SIB-R) Adaptive Behavior Short Form:								
Raw score	27	82.6 ± 12.9	25	84.3 ± 11.8	0.67	22	85.4 ± 12.5	0.33
Modified DOTS task:								
Mean correct cats	-	-	25	0.43 ± 0.14	-	23	0.40 ± 0.15	0.94 ***
Mean correct frogs	-	-	25	0.41 ± 0.12	-	23	0.43 ± 0.13	0.08 ***
Mean correct combined	-	-	25	0.41 ± 0.09	-	23	0.40 ± 0.13	0.29 ***
CANTAB Paired Associates Learning (PAL):								
Mean errors to success	27	4.9 ± 3.2	24	4.5 ± 3.3	0.99	22	4.5 ± 3.8	0.44
First trial memory score	28	10.6 ± 6.0	26	12.3 ± 6.7	0.02	24	12.0 ± 6.6	0.24
CANTAL Simple Reaction Time (SRT):								
Mean correct latency (ms)	28	582.1 ± 324.3	26	585.2 ± 299.0	0.74	24	599.1 ± 289.9	0.43

General health measures:								
EQ-5D:								
Mobility	28	0.0 (0.0-2.0)	26	0.0 (0.0-0.1)	1.00	24	0.0 (0.0-1.0)	1.00
Self-care	28	0.0 (0.0-1.0)	26	0.0 (0.0-1.0)	0.10	24	0.0 (0.0-1.0)	1.00
Usual activities	28	0.0 (0.0-1.8)	26	0.0 (0.0-0.0)	0.02	24	0.00 (0.00-0.75)	0.39
Pain/discomfort	28	0.5 (0.0-1.0)	26	0.0 (0.0-1.0)	0.02	24	0.00 (0.00-0.00)	0.07
Anxiety/depression	28	0.0 (0.0-1.0)	26	0.0 (0.0-0.0)	0.06	24	0.00 (0.00-0.75)	0.67
Health state (visual analogue scale; %)	27	81.0 ± 18.8	25	83.6 ± 19.1	0.45	24	84.6 ± 20.8	0.59
RAND SF-36:								
Total percent	28	67.5 ± 21.0	26	71.8 ± 17.0	0.01	23	75.9 ± 15.7	0.02
Physical functioning	27	68.3 ± 31.3	25	73.0 ± 30.3	<0.0001	22	77.8 ± 27.3	0.03
Role limitations due to physical health	28	100.0 (75.0-100.0)	26	100 (93.8-100.0)	0.19	23	100.0 (100.0-100.0)	0.21
Role limitations due to emotional problems	28	100.0 (100.0-100.0)	26	100.0 (100.0-100.0)	0.10	23	100.0 (100.0-100.0)	1.00
Energy/fatigue	28	50.2 ± 21.0	26	51.9 ± 18.8	0.44	23	59.3 ± 20.2	0.14
Emotional well-being	5	67.2 ± 22.7	5	80.8 ± 13.7	0.25	4	86.0 ± 15.5	0.21
Social functioning	27	84.3 ± 20.7	26	86.1 ± 21.3	0.55	23	84.2 ± 20.0	0.77
Pain	28	61.6 ± 23.2	26	60.9 ± 19.0	0.66	23	60.3 ± 17.6	0.24
General health	28	73.8 ± 23.1	26	81.2 ± 16.9	0.02	23	83.7 ± 20.7	0.05
Carer-related measures:								
General Health Questionnaire 12-item version (GHQ12):								
Total score	27	10.6 ± 3.2	25	10.7 ± 5.8	0.95	22	10.6 ± 7.4	1.00
Modified carer burden inventory (CBI):								
Total score	27	9.9 ± 6.8	25	9.9 ± 7.3	0.60	22	9.3 ± 8.0	0.67

Table 41: Whole group sleep, behaviour and CPAP usage data across months 1-12 of the study. It should be noted that the lifestyle group commenced CPAP at the end of the 1 month visit, and so lifestyle group 1 month data was collected at an additional 1 month + 1 month visit and pooled with the CPAP group 1 month visit data. Significance of change assessed using paired sample t-tests versus change of 0 (i.e. no change).

*** Includes CPAP data from machine download of patient at withdrawal.**
**** No data due to machine error.**

	1 month post-CPAP initiation			3 month visit			6 month visit			12 month visit		
	n = 27			n = 26			n = 26 *			n = 25 *		
Participant characteristics	**Total included**	**Δ from baseline**	**p**	**Total included**	**Δ from baseline**	**p**	**Total included**	**Δ from baseline**	**p**	**Total included**	**Δ from baseline**	**p**
Developmental Behaviour Checklist for Adults (DBC-A):												
Disruptive behaviour subscale (scale range 0-34)	26	-1.38 ± 2.61	0.01	26	-2.65 ± 3.65	0.001	24	-2.50 ± 3.43	0.002	23	-3.13 ± 3.11	<0.0001
Anxiety/Antisocial subscale (scale range -2-14)	26	-0.58 ± 1.30	0.03	26	-0.54 ± 1.29	0.05	24	-0.42 ± 1.14	0.09	23	-0.48 ± 0.95	0.02
Depressive subscale (scale range 0-18)	26	-0.96 ± 2.24	0.04	26	-1.65 ± 2.94	0.01	24	-1.58 ± 2.87	0.01	23	-1.65 ± 2.66	0.01
Pictorial Epworth Sleepiness Scale (pESS):												
Self-rated	26	-1.27 ± 5.94	0.29	25	-4.36 ± 5.37	<0.0001	24	-4.75 ± 5.61	<0.0001	24	-4.75 ± 6.23	0.001
Carer-rated	21	-1.33 ± 5.58	0.29	19	-3.00 ± 4.97	0.02	17	-4.29 ± 6.57	0.02	16	-3.44 ± 5.70	0.03
Kaufmann Brief Intelligence Test (KBIT-2)												
Raw score verbal	25	3.20 ± 5.45	0.01	26	4.04 ± 5.99	0.002	25	3.88 ± 6.55	0.01	24	4.42 ± 5.88	0.001
Raw score non-verbal	25	5.16 ± 15.21	0.10	26	4.92 ± 12.15	0.05	25	4.92 ± 12.08	0.05	24	6.13 ± 14.79	0.05
Continuous positive airway pressure (CPAP):	**Total included**	**Raw value**	**p**	**Total included**	**Δ from 1 month**	**p**	**Total included**	**Δ from 1 month**	**p**	**Total included**	**Δ from 1 month**	**p**
Total days since CPAP initiation	-	34 ± 9	-	26	41.77 ± 20.76	-	26	127.81 ± 20.03	-	25	318.48 ± 17.11	-
Days used (%)	-	55.0 ± 34.5	-	26	-1.27 ± 12.3	0.61	26	0.10 ± 15.72	0.98	25	-3.80 ± 15.34	0.23
Days used ≥ 4hr (%)	-	35.7 (0.0-84.0)	-	26	-0.56 ± 6.43	0.66	26	1.70 ± 11.4	0.45	25	0.76 ± 15.96	0.81
Total usage (hr)	-	64.6 (8.2-143.3)	-	26	117.01 ± 147.14	-	26	358.3 ± 365.07	-	25	812.74 ± 808.27	-
Mean usage (hr)	-	1.7 (0.2-4.5)	-	26	-0.19 ± 1.15	0.41	26	-0.07 ± 1.21	0.79	25	-0.34 ± 1.25	0.18
Median usage (hr)	-	2.8 (1.1-6.7)	-	26	-0.04 ± 0.46	0.68	26	0.10 ± 0.76	0.51	25	0.04 ± 1.04	0.85
95th centile pressure (cmH2O)	-	8.2 ± 3.0	-	26	0.12 ± 1.4	-	26	0.16 ± 0.14	-	25	0.58 ± 1.79	-
95th centile leak (L/sec)	-	0.3 (0.2-0.5)	-	25 **	-0.04 ± 0.26	0.50	25 **	-0.12 ± 0.40	0.16	24 **	-0.20 ± 0.48	0.05
Apnoea/Hypopnoea index (derived from CPAP machine)	-	9.7 (1.2-11.8)	-	25 **	-0.23 ± 1.8	0.54	25 **	-0.66 ± 2.46	0.19	24 **	-1.10 ± 2.73	0.06

8.2.4.1 CPAP usage

At 1 month post-CPAP initiation (mean total days since initiation 39±4 days), CPAP compliance across the whole group (n=27) was low, with a mean usage of 1.7(0.2-4.5)hr/night and median usage of 2.8(1.1-6.7)hr/night. CPAP was used on 55±35% of days, and the mean proportion of used days where CPAP was used for ≥4hr was 35.7(0.0-84.0)%. The mean total hours used was 64.6(8.2-143.3)hr. The mean 95th centile pressure was 8.2±3.0cmH_2O and the 95th centile leak was within normal limits at 0.3(0.2-0.5)L/min. The mean machine-derived AHI was 9.7(1.2-11.8)/hr in bed (an AHI <5 is considered normal (Scottish Intercollegiate Guidelines Network 2003)).

No significant changes were noted with respect to compliance, pressure, leak or AHI at 3 month, 6 months or 12 months post-CPAP initiation (see Table 41). Mean compliance at 12 months (352±17 days from CPAP initiation) remained low: mean usage 1.5(0.3-4.6)hr/night; median usage 2.3(01.0-6.4)hr/night; days used 53.7±33.7%; used days ≥4hr 34.3(4.1-83.3)% (all n=25). The mean 95th centile pressure was 8.6±2.2cmH_2O, and the 95th centile leak was 0.3±0.2L/min. The mean AHI was 6.7(2.9-8.7)/hr in bed.

Correlation and regression analysis did not reveal any significant associations between age, gender, BMI, AH, ODI, behaviour or sleepiness at baseline with CPAP compliance at 12 months (data not shown).

All participants were fitted with full face masks: 14 commenced CPAP using a ResMed Mirage Quattro™ mask (extra small or small), 13 using a ResMed Quattro™ FX mask (extra small or small) and 1 using a Respironics Amara mask (petite). Eight participants required a change of mask during the trial; the majority switched from the ResMed Mirage Quattro™ to ResMed Quattro™ FX (n=5), with 3 switching from FX to Mirage and one individual switching from FX to Mirage and back to FX by the end of the study. No significant differences in usage, compliance, pressure, leak or AHI were noted between the mask types at 12 months (data not shown).

8.2.4.1.1 Adverse events

CPAP was generally well-tolerated, with only minor adverse events reported.

At 1 month, one participant reported skin irritation from the mask and another anxiety or fear related to the CPAP equipment. One participant was withdrawn from the study due to inability to tolerate CPAP.

At 3 months, a further participant had withdrawn from the study due to inability to tolerate CPAP and 9 individuals (35%) reported adverse events. These included anxiety/fear of CPAP (12%), inability to tolerate CPAP (8%), mask leak (8%), wakening due to CPAP (4%) and nasal congestion (4%).

Twenty-eight percent of participants reported adverse events at 6 months, including dry mouth (8%), respiratory infection (8%), skin irritation, anxiety/fear of CPAP and inability to tolerate CPAP (all 4%).

By 12 months, 24 participants remained in the study, with 2 participants withdrawn due to close family bereavement and moving into residential care respectively. Six participants (25%) reported adverse events: anxiety/fear of CPAP (8%); inability to tolerate CPAP (8%); skin irritation (4%); wakening due to CPAP (4%). Of the 24 individuals remaining in the study, 25% reported that they were not using CPAP at the time of the 12 months visit. Half of these reported not using CPAP due to a dislike of CPAP, one was afraid of CPAP, one felt their symptoms had improved and so no longer wished to use CPAP and one parent was unwilling to continue CPAP.

Nineteen individuals (79% of those completing the study) elected to continue using CPAP at the end of the study period. Of the 5 individuals who returned their machines, two were unable to tolerate CPAP, 2 did not like CPAP and one refused to use the treatment.

8.2.4.1.2 Humidification

Humidification was commenced as required based on reported symptoms, such as nasal congestion or dryness, and the unblinded investigator's clinical judgement. Two individuals (7%) used humidification at 1 month, 4 (15%) at 3 months, 7 (28%)

at 6 months and 7 (29%) at 12 months. No significant differences were evident in CPAP outcomes between those using humidification and those without (data not shown).

8.2.4.2 Anthropometric characteristics

BMI and collar size did not vary significantly across the study, as evidenced in Table 40.

8.2.4.3 Subjective sleepiness

As shown in Table 40 and Table 41, mean self-rated pESS scores improved significantly across the 12 month study period, falling from 11±6 at baseline to 7±6 at 3 months ($p<0.0001$) 6±5 at 12 months ($p=0.001$). The mean self-rated pESS from baseline was not significantly reduced at 1 month post-CPAP initiation, but the mean Δ in pESS showed a significant reduction in subjective sleepiness at 3 months (-4.4±5.4; $p<0.0001$), which was sustained at 6 (-4.8±5.6; $p<0.0001$) and 12 months ($p=0.001$). There was an overall downward trend in proxy-rated pESS scores with 1 month ($p=0.29$), 3 months ($p=0.02$), 6 months ($p=0.02$) and 12 months ($p=0.03$) on CPAP, although this did not reach significance.

8.2.4.4 Behavioural and emotional disturbances

As shown in Table 40, a significant decrease in DBC-A Disruptive subscale raw scores was observed at 12 months in comparison to baseline, indicating an overall improvement in Disruptive behaviour (1(0-3) v. 4 (2-8); $p<0.0001$). Disruptive MIS and PIC scores were also significantly reduces (both $p<0.0001$), indicating a reduction in both the severity of behavioural/emotional disturbance and the breadth of problem behaviours. Similar reductions were also noted in Depressive behaviour raw, MIS and PIC scores (all $p=0.001$). No significant change was evident in Anxiety/Antisocial behaviour scores, though scores remained very low throughout the study.

Change (Δ) in behaviour scores is summarised in Table 41. A downward trend in scores on the Anxiety/Antisocial and Depressive subscale raw scores was observed across the 12 month study period, but did not reach the conservative significance

threshold for this trial. Raw scores in the Disruptive behaviour domain also exhibited a steady reduction from baseline, reaching significance at 3 months (p=0.001) and 12 months (p<0.0001).

8.2.4.5 Cognitive function

ACTB scores at baseline, 3 months and 12 months are shown in Table 40. The change in scores across the study is summarised in Table 41.

8.2.4.5.1 KBIT-2

Raw scores in the verbal domain of the KBIT-2 showed a significant improvement 12 months (p=0.001), with a trend towards improvement at 3 months (p=0.002). The mean baseline verbal score was 31±15, of a possible total of 108, rising to 37±19 at the 12 month visit. Non-verbal subscale scores were increased at 3 and 12 months but did not reach significance (p=0.05, p=0.01 respectively). The mean baseline score in this subscale was 13±5 of a possible 4, rising to 20±17 at 12 months.

When Δ values were compared to baseline, a sustained increase in verbal scores was noted, reaching significance at 12 months (p=0.001). Increases in non-verbal scores were observed across the study, but, again, did not reach significance.

8.2.4.5.2 SIB-R

The mean raw score on the SIB-R at baseline was 82.6±12.9 from a possible total of 120, and did not change significantly with CPAP use. An average, typically-developing adult aged 30 years achieves a score of 117/120 (Bruininks et al. 2006).

8.2.4.5.3 Modified Dots task

Data for the modified Dots task was overwritten due to operator error, and so no baseline data were available. However, the University of Arizona were able to recover data for the majority of patients for visits 4 and 7 only. No significant differences were noted between groups at visit 4, or between visit 4 and 7.

8.2.4.5.4 CANTAB PAL

No significant differences in the mean number of errors to success or first trial memory score on the CANTAB PAL test were noted (4.9±3.2 and 10.6±6.0 at baseline respectively).

8.2.4.5.5 CANTAB SRT

No significant improvement or decrement in reaction time scores was evident, with a mean correct latency of 582.1±324.3ms recorded at baseline.

8.2.4.6 General health measures

8.2.4.6.1 EQ-5D

The overall mean health state of participants as rated by the EQ-5D visual analogue scale was 81±19% at baseline, and this did not differ significantly across the study, despite CPAP use. Reported problems with mobility, self-care, carrying out usual activities, pain/discomfort and anxiety/depression were all low at baseline (Table 40), and did not vary significantly across the 12 months of the study.

8.2.4.6.2 RAND SF-36

RAND SF-36 scores at baseline, 3 months and 12 months are summarised in Table 40. The total percentage score was 68±21% at baseline, and was increased at 3 months and 12 months, though this did not reach significance ($p=0.01$ and $p=0.02$ respectively). Physical functioning increased significantly from baseline (68±31%) to 3 months (73±30%; $p<0.0001$). A further increase at 12 months was noted (78±27%), but this did not reach significance ($p=0.03$). General health increased from 74±23% at baseline to 84±21% at 12 months, but, again, this change was not significant in this small cohort ($p=0.02$ at 3 months, $p=0.05$ at 12 months).

No significant changes were evident in physical or emotional role limitation, energy/fatigue, emotional wellbeing, social functioning or pain as measured by the RAND SF-36. Notably, energy/fatigue scores were low in this population at baseline, with a mean score of 50±21%. This rose to 59±20% after 12 months on CPAP, but this was not significant ($p=0.14$).

The low number of participants with RAND SF-36 emotional wellbeing scores should be noted (n=5 at baseline and 3 months, and n= 4 at 12 months). The printed questionnaire issued to participants in the early stages of the study omitted a question used in calculation of this score in error (question 28: “Have you felt downhearted and blue?”), resulting in missing data for the majority of participants and rendering outcomes for this domain invalid.

8.2.4.7 Carer burden

8.2.4.7.1 Modified ZBI

Scores on the modified ZBI remained stable across the 12 month study period, averaging 10±7 of a possible 48 at baseline, with no significant change was noted. Higher scores indicate an increased burden of caring.

8.2.4.7.2 GHQ-12

At baseline, carers' mean baseline rating of their own general health was 11±3 out of a possible score of 36, with higher scores indicating a greater level of health impairment. This did not vary significantly during the 12 months of the study.

8.3 Discussion

This is the first randomised, controlled trial of CPAP therapy in adults with DS. Despite being underpowered due to small participant numbers, real and significant improvements in sleepiness, behaviour and daytime cognitive function were demonstrated, even with only modest use of CPAP.

To date, no other studies have formally evaluated the use of CPAP in adults with DS. Trois et al reported informally on the treatment of the individuals who had abnormal sleep studies as an aside to their prevalence study (Trois et al. 2009). Nine of the 14 adults with DS referred for CPAP treatment were followed up by the researchers, one sought treatment elsewhere and the follow-up status of the remaining 4 participants was not known. This study suggests that CPAP was acceptable to the majority of adults with DS, with over half of the individuals followed up using therapy for 6-8hr/night; the families of these adults with DS reported subjective improvements in sleepiness and daytime function. Two individuals did not accept CPAP, one quit due to side effects and one used CPAP for only <2hr/night. However, no formal assessment of sleepiness, daytime function, cognition or behaviour was undertaken in this very small group of adults with DS and OSAHS, and no standard methodology for CPAP initiation and support was described. The only other literature relating to the use of CPAP in individuals with DS focusses on children,

which cannot be generalised to the adult population, given the differences in OSAHS risk factors between these two groups.

There is a wealth of evidence that CPAP improves cognitive function and behaviour in the general population, as reviewed in Chapter 2, but much less is known in the DS population. A study of the effects of CPAP on neurobehavioural outcomes in 52children with OSAHS included a subset of 10 individuals with developmental delays, 6 of whom had DS (Marcus et al. 2012). Significant improvements in ESS, behaviour and quality of life were reported, despite the very small number of individuals in this group, and a similar finding was noted in the current study in adults with DS.

The AH requirement for entry to the treatment phase of this study was AH≥10 per hour in bed, lower than the generally-accepted diagnostic threshold (Scottish Intercollegiate Guidelines Network 2003). Studies in the general population have assessed the efficacy of treating mild OSAHS with CPAP, with two placebo-controlled studies of symptomatic individuals with an AHI in the mild range (5.0-14.9 events per hour) demonstrating improvements in sleepiness, mood and daytime function, even with low CPAP compliance (Engleman et al. 1997; Engleman et al. 1999). As discussed in Chapter 3, adults with DS may be more sensitive to the cognitive effects of untreated OSAHS given the existing cognitively impairment seen in this group, and so may stand to benefit even when diagnosed with only mild OSAHS (Beebe & Gozal 2002; Fernandez & Edgin 2013).

Although no significant differences were noted in the ACTB tests with CPAP use, this study has further validated the use of the ACTB in adults with DS. We have demonstrated that individuals with DS and moderate to severe ID can perform the tests in both home and hospital settings, confirming previous findings (Edgin et al. 2010).

There are a number of limitations to this study. Funding issues forced early closure of recruitment, which resulted in underpowering of the study, with only 28 of a projected 68 participants enrolled. It is of note that a further 67 individuals were

eligible to participate, but could not be enrolled due to lack of funding related to the delay in receiving ethical approval for the study as discussed in Chapter 4. However, this is still, to date, the largest study of CPAP in adults with DS reported worldwide. Moreover, despite the small number of participants and our conservative threshold for significance, statistically significant improvements in sleepiness, behaviour and cognitive function have been demonstrated. These positive results, alongside trends towards significant improvement in other domains, suggest that a larger trial may be of merit. Future studies may benefit from employing a multicentre design, allowing easier recruitment of the required numbers across the whole of the UK.

No significant differences in outcomes were evident after the one month randomised phase of the study. One month was selected as this length of time has been sufficient to show a significant change in the general population (Engleman et al. 1997; Engleman et al. 1999; McArdle et al. 2001; Robinson 2006; McArdle et al. 2010), and was felt to be the maximum time for which CPAP treatment could ethically be delayed. It may be that a longer randomised phase may have been optimal – other studies in the general population have used periods ranging from 6 weeks to 12 months (Engleman et al. 1993; McFadyen et al. 2001; Antic et al. 2011; Sivam et al. 2012; McMillan et al. 2014) – though perhaps unacceptable to the ethics committee.

Since all participants in this phase of the study had either moderate or severe ID, results may not be generalisable to the DS population as a whole. No significant differences were observed between those with capacity to give consent and AWI, though numbers were small. Future studies should, if possible, include adults with mild and profound ID, in large enough numbers to allow comparison across the spectrum of ability seen in individuals with DS. This may, however, prove difficult given the ethical issues faced when conducting research in AWI, as discussed in Chapter 4.

Problems with mask fit and comfort were encountered during this study, with many of the commercially-available CPAP interfaces proving to be too large for participants, even in the smallest sizes. All participants were fitted with full face masks due to obligate mouth breathing, related to relative macroglossia and

adenoidal facies. A recent study in the general population suggested that use of a full-face mask impacts negatively on compliance (Borel et al. 2013). Masks designed specifically for individuals with DS, taking into account the midface hypoplasia which is common in DS, may be required, and recent advances in 3D printing technology (Ventola 2014), may allow personalised masks modelled on each individual's face to become an option in the near future. Further research in this area is required.

It is usual clinical practice within the department to introduce heated humidification only as required in the event of side effects to CPAP such as nasal congestion or dryness, and so a similar approach was taken in this study. With hindsight, given the known issues of increased mucus secretion and frequent respiratory tract infections in individuals with DS (see Chapter 1), it may have been appropriate to start all participants on CPAP with humidification from day 1. There is conflicting evidence as to whether humidification improves CPAP compliance, with some studies showing a significant improvement (Massie et al. 1999; Neill et al. 2003) and others not (Worsnop et al. 2010). Although some participants did report side effects and were later issued with humidification, it is possible that this contributed to the poor compliance noted. A study of fixed versus auto-titrating CPAP in the general population noted a significant order effect, with neither type of device improving compliance but participants preferring whichever they used first (Vennelle et al. 2010); it is possible that a similar effect might be apparent with humidification, and so it may have been beneficial to commence humidification to all participants at the time of CPAP initiation.

The majority of participants in our study lived at home with their parent/carer, and so, again, results may not be generalisable to the adults DS population as a whole. Given that residential status can impact on a number of outcomes in people with DS as discussed elsewhere in this thesis, future research should include individuals living in supported accommodation and residential care settings, in sufficient numbers to allow comparison and to control for differences between these groups.

Given the small sample size, it was not viable to undertake the planned health economic analysis. However, we have, for the first time, demonstrated the utility of the EQ-5D instrument in adults with DS, and a larger trial to assess the health economic benefits of CPAP in this population is required. Health economic benefits of CPAP use have been demonstrated in older adults in the general population, despite modest compliance (McMillan et al. 2014).

Changes were noted in pESS, KBIT-2 and DBC-A scores despite a low median usage across the group, and it would be of interest to see whether these effects are amplified and if other measures show improvement in a dose-dependent manner. Although steps were taken in this study to encourage CPAP usage, future studies may wish to employ additional strategies to increase compliance. Cognitive behavioural interventions, self-management, peer support and intensive education and follow-up have all been shown to improve CPAP compliance in the general population (Hoy et al. 1999; Engleman & Wild 2003; Stepnowsky et al. 2007; Damjanovic et al. 2009; Parthasarathy et al. 2013; Wozniak et al. 2014), and incentivisation via token economy has been shown to increase adherence to physical activity programmes in individuals with DS (Bennett et al. 1989), offering many avenues to explore in future studies.

Reasons for continuing or quitting CPAP therapy were diverse, and included both patient and parental concerns. It is impossible to assess all the possible factors influencing CPAP compliance, but future studies should consider areas such as parental support and perception of CPAP and social factors surrounding CPAP use; socioeconomic status has been noted to impact on compliance in the general population (Platt et al. 2009), and a number of studies in the general population have investigated predictors of CPAP compliance, including psychological profiles, behaviour styles, perceptions of CPAP and health beliefs, as well as spouse or family member involvement (Wild et al. 2004; Aloia et al. 2005; Olsen et al. 2008; Baron et al. 2011; Baron et al. 2012; Balachandran et al. 2013). However, this study has demonstrated that the majority of adults with DS can tolerate CPAP, with over half of those entering the study continuing after 12 months, and its use as a standard

treatment for OSAHS in this group should not be ruled out purely on the basis of a diagnosis of DS.

8.4 Conclusion

Despite small participant numbers, this first randomised, controlled trial of CPAP therapy in adults with DS demonstrated that CPAP use leads to sustained, significant improvements in subjective sleepiness, behavioural and emotional outcomes and cognitive function in a group of individuals exhibiting moderate/severe intellectual disability. It is possible that some of the cognitive impairment seen in adults with DS may be related to untreated OSAHS, and that treatment can lessen, if not reverse, some of this impairment. CPAP appears to be effective and well-tolerated in this population, and, 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.

Chapter 9 Discussion and final conclusions

9.1 Discussion

9.1.1 What is the prevalence of OSAHS in adults with DS in Scotland (and the UK)?

Prior to this study, the prevalence of OSAHS in DS was unclear and had not been reported adequately in any country. In this series of studies, we have, for the first time, documented the prevalence of OSAHS in a large population of adults with DS by both subjective and objective means.

Using a subjective, easy-read questionnaire, we contacted over 5000 adults with DS across all four nations of the UK, covering a wide geographic area and socioeconomic range. Using previously validated algorithms and based on a cohort of 1067 valid responders, the prevalence of OSAHS in adults aged ≥16 years with DS living in the UK is 35%, with no gender difference evident. This is significantly higher than the 2% of women and 4% of men reported to have OSAHS in the general population (Young et al. 1993). Even in comparison to the recently updated Wisconsin Sleep Cohort data, which estimates that 10-17% of men and 3-10% of women now have OSAHS (Peppard et al. 2013), this represents a significantly elevated risk of OSAHS in the adult DS population. However, the majority of participants in our study (69%) were aged 20-40 years; the Wisconsin data surveyed individuals aged 30-70 years, and so these prevalence data may not be comparable. Our prevalence of 35% is modest compared to the studies of Trois et al and Resta et al, who estimated an OSAHS prevalence of >80% in adults with DS in Italy and the USA. Although these studies used objective measures of OSAHS, the very small sample size in these studies (n=16 and n=6 respectively) must be taken into consideration (Resta et al. 2003; Trois et al. 2009).

The prevalence we have reported in adults is also lower than the 55% reported in children with DS in Spain (de Miguel-Díez et al. 2003). This may reflect differing

risk factors for and aetiology of OSAHS in children and adults with DS. In the general population, OSAHS affects around 6% of children and is related mostly to hypertrophy of the adenoids and tonsils in relation to size of the airways, particularly between the age of 2-8 years (Marcus et al. 2012; Tan et al. 2013), while, in adults, the problem is related more to gender, advancing age and obesity. It is likely that this is similar in children with DS, though compounded by hypotonia, which is worse in children with DS and becomes less pronounced in adults, and obesity, which is more prevalent in those with DS than in the general population. Although obesity is less of a risk factor for OSAHS in typically-developing, pre-pubescent, children than it is in adults, this may not be the case in children with DS.

The majority of responders in or study were young adults, and, given the increasing prevalence of OSAHS with age in the general population, it is possible that OSAHS prevalence may be even higher in older adults with DS. Declining cognitive function may be a factor in the paucity of older people responding to the questionnaire in this study. Older adults are more likely to be living in residential care, which may also have affected the response rate in this subpopulation. Future studies should seek to recruit more individuals with DS in the older age group to further explore the relationship between age and OSAHS in this population.

Responders were predominantly overweight or obese. Females had a higher mean BMI, as reported in previous studies (Melville et al. 2005; Melville et al. 2007), and also had a higher prevalence of thyroid dysfunction. A link between these has been noted in women, but not men, in the general population (Milionis & Milionis 2013). Poorly controlled hypothyroidism and the use of oral contraceptives, both associated with weight gain, may explain the difference in BMI between genders, though other factors may be involved and further investigation is required. Residential status is known to affect BMI. This may account for some of the difference in BMI between men and women, but this information was not collected as part of the questionnaire study.

Coincidentally, the opportunity arose to undertake a comparative study of prevalence of OSAHS in adults with DS in Scotland and Japan. This is the first international

study to compare self-reported symptoms of OSAHS in adults with DS. Subjective prevalence of OSAHS in 267 adults with DS in Scotland was 20%, and in 522 adults with DS in Japan was 14%. The overall prevalence of OSAHS in adults with DS was 16% across both countries. Given that ethnic differences in OSAHS prevalence exist in the general population, it is interesting to note that this was not evident in two ethnically distinct populations of adults with DS. This suggests that the characteristic craniofacial features of DS override differing ethnicity in terms of the risk of OSAHS. A limitation of the UK prevalence study is that specific information on ethnicity was not collected although Scotland has a largely homogeneous (96%) Caucasian population (Scottish Government 2014).

Women with DS had a higher mean BMI than men in Scotland, though this difference was not seen in Japan. The use of contraceptives in women with DS is rare in Japan, and may play a role in this observation. Overall, both men and women had significantly lower mean BMI in Japan than in Scotland. Raised BMI was a risk factor for sleepiness in Scotland but not Japan, even when using Asian-specific BMI thresholds. The reasons for this are unknown, but may be cultural, diet-related or due to differing distribution of body fat between Asian and Western populations (Wang et al. 1994; Ogce et al. 2008).

The reason for the differences observed between the subjective prevalence of OSAHS in the UK, Scottish and Japanese populations are unclear. Although the Scottish and Japanese prevalences did not differ significantly at 20% and 14% respectively (16% overall), this is much lower than the 35% seen in the UK as a whole. This may partly reflect methodological differences. In the UK study, symptoms were classified as occurring never, rarely/sometimes (1-2 nights per week) or often/frequently (≥3 nights per week), whereas, in the Japan/Scotland comparison study, the classification was never, sometimes (1-4 nights per week) or frequently (5-7 nights per week). The effects of residential status on these observations cannot be ascertained, as information on this was not collected.

The subjective nature of both the UK and Japan prevalence studies represents a clear limitation. However, we also collected objective prevalence data for OSA in a subset

of the questionnaire study participants using home polygraphy. Of a sample of 134 adults with DS, 56% met the criteria for probable OSAHS using the same algorithmic method of assessment employed in the questionnaire study. Forty-two percent of the subjects were diagnosed with OSAHS on using objective testing. OSAHS was defined as an AH≥15 per hour in bed plus symptoms (pESS>10, unrefreshing sleep ≥3 nights per week or daytime sleepiness ≥3 nights per week). This demonstrated that the algorithms utilised (Fuhrman et al. 2012) had good sensitivity (79%), but relatively poor specificity (59%). In line with the subjective prevalence study results, no gender difference in OSAHS prevalence was evident. Symptoms alone were not indicative of the severity of OSAHS, as defined by AH per hour in bed or ODI, reflecting similar observations in the general population.

The limitations of home polygraphy, including the absence of data on sleep architecture and dilution of the AHI, must be borne in mind. Nevertheless, the validity and cost-effectiveness of home polygraphy versus inpatient PSG has been demonstrated by previous studies (Dingli et al. 2003; Juan F. Masa et al. 2011), and current guidelines recommend this as the first-line diagnostic test for adults with a high clinical suspicion of OSAHS (Scottish Intercollegiate Guidelines Network 2003). We have demonstrated the tolerability and reliability of home polygraphy in a large group of adults with DS; it is of note that home polygraphy was tolerated by the majority of participants and a scoreable study was obtained in 90% of cases, 94% of these after only 1 or 2 nights of recording. Future studies may use smaller, more modern polygraphy equipment or ambulatory PSG with digital video to collect further information on sleep staging and quantification of sleep fragmentation via EEG arousal scoring.

In both the subjective and objective prevalence studies, probable or actual OSAHS was associated with worse behaviour scores in the Disruptive, Anxiety/Antisocial and Depressive subscales of the DBC-A, though these did not reach significance in the objective prevalence study with its smaller sample size and our strict threshold for significance. Behaviour scores were generally low, which is perhaps unsurprising given that individuals with DS exhibit a lower prevalence of maladaptive behaviours than those with ID of other aetiologies (Chapman & Hesketh 2000; Blacher &

McIntyre 2006). It may be that the DBC-A and/or the subscales selected are less sensitive in individuals with DS than others with ID. The absence of normative data for the version of the DBC-A used in this study makes this difficult to assess. However, differences in behaviour have been demonstrated and should be explored further in future studies with the same or alternative instruments.

9.1.2 Does CPAP use in DS adults with OSAHS improve sleepiness and quality of life more effectively than lifestyle measures alone?

This is the first RCT of CPAP therapy in adults with DS, and provides the first empirical evidence of improvement in sleepiness, behaviour and cognitive function in adults with DS and OSAHS.

No significant difference was noted between the CPAP and lifestyle groups after 1 month. This may be due to a number of factors, including the small number of participants (27 in total), low CPAP compliance (median usage 3.0(1.6-4.7) hr/night), and short duration to follow-up (1 month). Very low levels of impairment on subjective measures of behaviour, quality of life and general health may have left little room for improvement. Although RCTs of CPAP efficacy in the general population have shown an effect after 1 month (McFadyen et al. 2001; McArdle et al. 2001; Senn et al. 2003; Robinson 2006), a longer period may be required in individuals with DS. A larger sample size of sufficient power is also required.

However, despite these limitations, when the whole group was assessed after 12 months, significant and sustained improvements in Disruptive and Depressive behaviour scores, self-rated subjective sleepiness and verbal intelligence measured by the KBIT-2 were noted. Strong trends towards improvement in carer-rated sleepiness, Anxiety/Antisocial behaviour scores and KBIT-2 non-verbal intelligence scores were noted, but did not reach significance at the $p<0.001$ level. Interestingly, no change was noted in the ACTB measures of prefrontal, cerebellar or hippocampal function. This may, again, be related to the small number of participants in the study or, perhaps, the sensitivity of the tests selected from the battery. However, we have

further validated the acceptability and utility of the ACTB, and further examination in a larger trial is warranted.

9.1.3 What are the potential barriers to implementing CPAP effectively in DS adults with OSAHS?

CPAP compliance in our population was generally low. Over the first month on CPAP, participants used the machine on only 55±35% of nights, with a median usage of 2.8(1.1-6.7) hr/night. After 12 months, this had not changed significantly, with use on 54±34% of nights and a median usage of 2.3(1.0-6.4) hr/night. The reasons for this are unclear; despite some problems finding a suitable mask initially, the mean mask leak remained well within acceptable limits throughout the study. Very few side effects were reported, and these were in line with the general population: skin irritation; nasal congestion; dry mouth; respiratory infection; mask leak; wakening due to CPAP; and anxiety or fear of CPAP. Humidification was started only when required; given that individuals with DS often have increased mucus secretion and recurrent respiratory infections, there may be an indication to commence humidification in all adults with DS, although, in this study, the use of humidification did not result in any significant difference in outcomes.

Of the 28 participants enrolled in the study, 4 had withdrawn by 12 months. Of the 24 remaining at 12 months, 5 opted not to continue with CPAP. Of the 9 participants who quit CPAP, 7 did so because they could not tolerate CPAP, disliked CPAP or refused to use the machine. One withdrew due to a close family bereavement and another due to moving to residential care, and CPAP was withdrawn at the request of the parent. Of the 24 individuals completing the full 12 months of the trial, a quarter were not using CPAP at 12 months; half of these disliked CPAP, one no longer wished to use CPAP as their symptoms had improved and one parent was unwilling to continue with CPAP.

CPAP compliance and acceptance is variable in the general population, and this study in adults with DS has shown similar outcomes. Despite frequent follow-up and support, a proportion used CPAP infrequently or quit altogether. Further studies should assess the efficacy of techniques to improve CPAP compliance in this group,

such as specific behavioural interventions or, reward systems adapted to the level of ID. (Bennett et al. 1989; Engleman & Wild 2003). It may be that individuals with DS need more time, more intense support, more accessible information and more tailored interventions to improve compliance and acceptance of treatment. DS-specific CPAP interfaces would be beneficial. Our results suggest that the beliefs and perceptions of the parent/carer may also be important, and this is another area for investigation.

However, it is of note that over two thirds of individuals continued on CPAP at the end of the study, suggesting that CPAP is generally acceptable in this group and that benefits are perceived by the patients and/or their relatives/carers.

9.2 Future work and considerations

Although this series of studies addresses a number of gaps in the current evidence base relating to adults with DS and OSAHS, there is scope for further work.

With only 28 participants, the treatment phase of the study is underpowered. This was due to funding issues resulting from the one-year delay in recruitment due to difficulties gaining ethical approval to include adults with DS of all levels of ID in the study, as discussed in Section 4.5. The initial decision of the ethics committee to grant permission only to include adults with DS who had capacity to consent for themselves not only introduced a barrier to carrying out the study, but potentially limited the usefulness of the results, which would only be generalisable to the small population of high functioning adults with DS and not the majority of the population who present with moderate to severe ID. While this barrier was eventually overcome and permission was granted to include AWI, the commencement of the study was delayed and the catchment area of the trial had to be extended in an attempt to recruit the minimum number of participants required. This delay to the start of the study, coupled with the additional time and expense of visiting participants over a much larger geographical area, meant that the study was not complete by the end of the funding period and a further 67 individuals who were eligible to participate in the study could not be enrolled. Many of these individuals went on to start CPAP

outwith the study through their local clinical service, and, while it is appropriate that they receive treatment, it is somewhat frustrating to be unable to include their data and experience of CPAP use within this study.

However, despite being underpowered, this study has shown real, significant and sustained improvements in sleepiness, behaviour and daytime function, and has demonstrated that adults with DS can both tolerate and benefit from CPAP therapy for OSAHS. This provides the first evidence to support a larger randomised, controlled trial of CPAP in this population. Given the logistical difficulties in recruiting to the study due to the large geographical area covered, it would be sensible for the next study to be of multicentre design. We have demonstrated that individuals from all parts of the UK are interested in research participation, and that ambulatory sleep studies conducted by individuals and their relatives/carers at home are feasible.

This first randomised trial of CPAP in adults with DS and OSAHS has shown that this patient population can tolerate CPAP, although compliance was low. Further investigation of the barriers to CPAP use are required. It is likely that these are multifactorial, and related to the relative/carer of the individual with DS as well as the patient themselves. A number of studies in the general population have shown that CPAP compliance is related to a number of psychological factors including health beliefs, behaviour models and self-efficacy; in adults with DS, these factors might apply to both the patient themselves and the people who support them. Elucidation of these barriers would allow CPAP initiation and support to be tailored to the individual needs of the person with DS and their family, potentially improving compliance and treatment outcomes. The development of an evidence-based pathway for CPAP education, initiation and follow-up in adults with DS which could be rolled out in sleep centres would improve the availability of suitable services for adults with DS and OSAHS, and would be a step towards reducing some of the health inequalities experienced by individuals with DS generally. Mask fit was an issue in this study, and “DS-friendly” masks, designed to fit the common craniofacial phenotype of DS, minimise skin irritation and be aesthetically acceptable to a “medical-phobic” group would certainly be ideal.

Dementia was an exclusion criterion for this treatment study. However, as discussed, early-onset dementia is common in adults with DS, and untreated OSAHS may accelerate the cognitive decline seen in this group (Fernandez & Edgin 2013). Therefore, a trial of CPAP therapy in adults with DS and dementia to assess the effect of treating OSAHS on the symptoms of dementia is warranted. Studies in individuals with Alzheimer disease and OSAHS in the general population have shown that these patients can tolerate CPAP, and that its use is associated with improvements in sleepiness, cognitive function, depressive symptoms and behaviour; the sleep quality of caregivers was also improved (Chong et al. 2006; Ayalon et al. 2006; Ancoli-Israel et al. 2008; Cooke et al. 2009). Given the increasing life expectancy of adults with DS, coupled with the high prevalence of dementia in this group, treating OSAHS may result in not only improved health and quality of live for individuals and their carers, but also health economic benefits.

The subjective and objective data presented here, as well as other published studies (Capone et al. 2013), suggest that adenotonsillectomy in children with DS may not confer sustained treatment of OSAHS into adulthood. A prospective study following children with DS and OSAHS into adulthood, pre- and post-adenotonsillectomy, would be of great value, documenting the natural history of OSAHS in individuals with DS across the lifespan and examining the potential factors influencing the efficacy of adenotonsillectomy in this group.

We have shown that the pESS can be used effectively in adults with DS, though with some drawbacks relating to specific questions related to reading, driving and lying down in the afternoon. A modified version of the pESS, designed specifically for individuals with DS and ID in mind, would improve the utility of this measure in this specific patient population. The use of easy-read and pictorial questionnaires and information in sleep centres and other clinical settings would be another avenue whereby health inequality in people with DS and ID of other causes could be better addressed.

9.3 Final conclusions and clinical implications

Prior to the commencement of this study, the prevalence of OSAHS in adults with DS was unclear, based on two very small studies (n=22 in total), with no published studies of the efficacy of CPAP treatment in this population available.

This study has demonstrated that the prevalence of OSAHS in adults with DS in the UK is approximately 40%, using subjective and objective methods in a large population-based cohort (n=1067 subjective prevalence, n=134 objective prevalence). Comparison of subjective prevalence in Scotland and Japan found no significant differences between countries of differing ethnicity, albeit with a lower estimated prevalence of 15-20%.

Furthermore, this study has shown that CPAP therapy is both tolerated and effective in adults with DS, even in a relatively small group (n=28). This work provides the first evidence to support the use of CPAP in adults with DS and OSAHS, whilst laying the foundations for further, large-scale trials.

The study has a number of clinical implications. The extent of OSAHS in adults with DS been quantified for the first time in a large cohort, highlighting the need for individuals, carers and healthcare professionals to be vigilant for symptoms of OSAHS in this group. This work suggests that, in adults with DS, we must not only consider the symptoms typically associated with untreated OSAHS in adults (such as EDS, snoring and witnessed apnoeas), but additional features such as behavioural and emotional disturbances. Instruments which are commonly used to assess sleepiness and general health in the general population, such as the (p)ESS and EQ-5D, have been shown to be of use in the adult DS population, although these may require adaptation to increase their utility in this group. This is particularly true for the pESS, where adaptation of the questions used to more adequately reflect daily living in adults with DS (or amendment of the diagnostic threshold) may improve the clinical value of the questionnaire. The feasibility of home-based diagnostic testing in this population has been demonstrated, offering a low-cost and easy-to-use option for OSAHS screening in adults with DS. Finally, although limited by the small number of participants, this study offers the first formal evidence that, with adequate

support, adults with DS can tolerate CPAP and gain long-term health benefits with even modest use. It is hoped that these findings, and those of further large scale, multi-centre trials, will inform future guidelines for screening, diagnosis and treatment on OSAHS in adults with DS in the UK and beyond.

In this study, only 3% of responders surveyed had a prior diagnosis of OSAHS, despite a likely prevalence over ten times higher than this. It is hoped that the results of this study will increase awareness of OSAHS in adults with DS, highlighting that poor sleep is not "just part of the condition", but is, in fact, a common comorbidity of DS which can be successfully treated in most cases, leading to benefits not just in terms of more settled sleep, but in daytime function and behaviour. Screening for OSAHS should form a standard component of ongoing health surveillance in adults with DS.

With an increase in individuals and families seeking diagnosis and treatment of OSAHS, healthcare providers must make efforts to make their services more inclusive, providing care and support that is acceptable to and effective for individuals with DS. Literature must be provided in easy-read format, and the location and duration of appointments must be tailored to this group. Additional support from healthcare staff may be necessary to successfully initiate and maintain the use of CPAP therapy in adults with DS. Of course, this may have budgetary and staffing implications, and further studies on the health economic benefits of CPAP in adults with DS are required.

In conclusion, OSAHS is a common disorder in adults with DS, affecting more than one in three individuals. However, with the appropriate care and support, OSAHS can be treated effectively, improving daytime function and behaviour. Testing and treatment should be routinely offered to all adults with DS; it is hoped that this study provides a first step towards this becoming common practice.

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Appendix 1 - Questionnaire study documents

Invitation letter

Invitation leaflet

Prevalence questionnaire

Appendix 2 – Sleep study documents

Invitation letter

Letter re. inclusion of adults with incapacity

Information sheets

- **Participant**
- **Parent/carer**
- **Adults with incapacity**

Reply slip

Consent forms

- **Participant**
- **Carer**

Sleep study instruction sheet

Sample sleep study report

Results letters

Home study completion letter

Appendix 3 – Treatment study documents

GP letters

- **Study commencement**
- **Study completion**
- **Study withdrawal**

Study contact information

Lifestyle advice

OSAHS information sheets

- **Participant**
- **Parent/carer**

Monthly diary

CRFs

- **Blinded investigator**
- **Second blinded investigator**
- **Unblinded investigator**

Participant questionnaires

- **Healthcare contact**

Carer questionnaires

- **Modified ZBI**
- **DBC-A**
- **Qualitative questions**

Appendix 4 – Publications, presentations and awards arising from thesis

Manuscripts under submission

Hill EA, Williams L, Cooper S, Riha RL. Obstructive sleep apnoea/hypopnoea syndrome in UK adults with Down syndrome: a cross-sectional prevalence study. *In submission.*

Hill EA, Sawatari H, Nishizaka M, Fairley DM, Chishaki A, Riha RL, Ando S. Symptoms of obstructive sleep apnoea in adults with Down syndrome in Scotland and Japan. *In submission.*

Accepted abstracts

Hill EA, Van Putten S, Cooper S, Williams L, Riha RL. Obstructive sleep apnoea in adults with Down syndrome: a cross-sectional prevalence study. 7th World Congress of the World Sleep Federation, Istanbul, 2015.

Hill EA, Williams L, Riha RL. Symptoms of obstructive sleep apnoea are common in adults with Down syndrome despite previous adenoid/tonsillar surgery. British Sleep Society Scientific Meeting, Newcastle, 2015.

Hill EA, Fairley DM, Williams LJ, Cooper S-A, Riha RL. A prospective, randomised, controlled trial of CPAP in adults with Down syndrome. *European Respiratory Journal* 2015; 46: Suppl. 59, 497.

Sawatari H, Hill EA, Nishizaka MK, Fairley D, Chishaki A, Ando S, Riha RL. Comparison of signs related to sleep disordered breathing among adult people with Down syndrome between two different races, Japanese and Scottish. *Somnologie* 2015; (suppl 1) 19:4–45

Hill EA, Sawatari H, Fairley DM, Nishizaka M, Chishaki A, Riha RL, Ando S. Sleep-disordered breathing, sleepiness and behavioural/emotional disturbance in people Down syndrome. UK and Europe Down Syndrome Research Forum, Bristol, 2013.

Sawatari H, Hill E, Nishizaka M, Chisaki A, Riha R, Ando S. Sleep-disordered breathing in adults with Down syndrome: a cross cultural comparison. *Sleep Medicine* 2013; 14(suppl.): e260.

Hill EA, Fairley D, Van Putten S, Cooper S, Forbes JF, Williams L, Riha RL. Use of the pictorial Epworth Sleepiness Scale in adults with Down's syndrome. *Journal of Sleep Research* 2012; 21 (suppl.1): 291.

Hill EA, Fairley D, Van Putten S, Cooper S, Forbes JF, Williams L, Riha RL. Prevalence of sleep apnoea, sleepiness and behavioural/emotional disturbances in adults with Down's syndrome in Scotland. *European Respiratory Journal* 2012; 40 (suppl.56): 325s.

Hill EA, Fairley D, Van Putten S, Cooper SA, Forbes JF, Williams L, Riha RL. Prevalence of sleep-disordered breathing in adults with Down's Syndrome in Scotland. *SLEEP* 2012; 35(suppl.):A18.

Hill EA, Fairley D, Van Putten S, Cooper SA, Forbes JF, Williams L, Riha RL. Snoring, sleepiness and behavioural correlates in Scottish adults with Down's Syndrome. World Down Syndrome Congress, Cape Town, 2012

Awards

2015 World Sleep Federation / European Sleep Research Society WSF2015 Travel Grant.

2015 European Respiratory Society Travel Grant for Sleep Medicine 2015.

Invited speaker

Obstructive sleep apnoea and behavioural and emotional disturbances in adults with Down syndrome. In symposium: Sleep and daytime function in developmental disorders, 7th World Congress of the World Sleep Federation, Istanbul, 2015.

Sleep-disordered breathing in Down's syndrome. British Sleep Society 25th Anniversary Scientific Meeting, Edinburgh, 2013.

Sleep-disordered breathing, sleepiness and behavioural/emotional disturbance in people with Down syndrome. Royal Hospital For Sick Children Respiratory/Sleep department research meeting, 2013.

Sleep apnoea workshop. Down's Syndrome Scotland conference, Cumbernauld, 2012.

Sleep & Down's Syndrome. European Society of Sleep Technologists Congress, Paris, 2012.

Prevalence and treatment of sleep apnoea in adults with Down syndrome: Introduction and preliminary data. Down Syndrome Medical Interest Group (UK and Ireland) One day symposium and members' meeting, Winchester, 2012.

Snoring, sleepiness & behavioural correlates in people with Down's Syndrome. Departmental meeting, Glasgow Sleep Centre, 2011.

Web articles

Hill EA. Sleep-disordered breathing and Down's Syndrome. Scottish Association for Sleep Apnoea (www.scottishsleepapnoea.co.uk), 2015.

Hill EA. Annual Health Check Information for GPs: Sleep Problems. Down's Syndrome Association (www.dshealth.org), 2013, updated 2015.

Other articles

Hill EA. Sleep apnoea in adults with Down syndrome: an update. Full Potential (Down's Syndrome Scotland magazine), 2015.

Hill EA. Sleep-disordered breathing and Down syndrome – what you need to know. Down's Heart Group Newsletter, 2015.