

Prevalence and predictors of obstructive sleep apnoea in young children with Down syndrome

Hill, Catherine, Evans, Hazel J., Elphick, Heather, Farquhar, Michael, Pickering, Ruth, Kingshott, Ruth, Martin, Jane, Reynolds, Janine, Joyce, Anna, Rush, Carla, Gavlak, Johanna C. and Gringas, Paul

Author post-print (accepted) deposited by Coventry University's Repository

Original citation & hyperlink:

Hill, Catherine M., et al. "Prevalence and predictors of obstructive sleep apnoea in young children with Down syndrome." *Sleep medicine* 27 (2016): 99-106.

<https://dx.doi.org/10.1016/j.sleep.2016.10.001>

ISSN 1389-9457

ESSN 1878-5506

Publisher: Elsevier

NOTICE: this is the author's version of a work that was accepted for publication in *Sleep medicine*. Changes resulting from the publishing process, such as peer review, editing, corrections, structural formatting, and other quality control mechanisms may not be reflected in this document. Changes may have been made to this work since it was submitted for publication. A definitive version was subsequently published in *Sleep Medicine*, Volume 27-28 (2016) DOI: 10.1016/j.sleep.2016.10.001

© 2016, Elsevier. Licensed under the Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International

<http://creativecommons.org/licenses/by-nc-nd/4.0/>

Copyright © and Moral Rights are retained by the author(s) and/ or other copyright owners. A copy can be downloaded for personal non-commercial research or study, without prior permission or charge. This item cannot be reproduced or quoted extensively from without first obtaining permission in writing from the copyright holder(s). The content must not be changed in any way or sold commercially in any format or medium without the formal permission of the copyright holders.

This document is the author's post-print version, incorporating any revisions agreed during the peer-review process. Some differences between the published version and this version may remain and you are advised to consult the published version if you wish to cite from it.

Prevalence and predictors of obstructive sleep apnea in young children with Down syndrome

Catherine M Hill,^{1,2} Hazel Evans,² Heather Elphick,³ Michael Farquhar,⁵ Ruth M Pickering¹,
Ruth Kingshott³, Jane Martin⁴, Janine Reynolds³, Anna Joyce,⁵ Carla Rush⁵, Johanna
Gavlak¹, Paul Gringras.⁵

Corresponding author.

Dr Catherine Mary Hill. BM MSc MRCP FRCPCH ES

Associate Professor of Child Health

Honorary Consultant in Paediatric Sleep Medicine

Division of Clinical Experimental Sciences

Mail point 803CB, G-Level, University Hospital Southampton

Tremona Road, Southampton, SO16 6YD, United Kingdom

Fax +4423 8120 6420; Tel +4423 8120 6091, e mail cmh2@soton.ac.uk

Word count: main body of text: 4151 words

¹ University of Southampton, UK

² Southampton Children's Hospital, Southampton University Hospitals NHS Trust

³ Sheffield Children's Hospital NHS Foundation Trust, UK

⁴ Southampton Centre for Biomedical Research, Southampton University Hospitals NHS Trust, UK

⁵ Evelina London Children's Hospital, Guys St Thomas's NHS Trust, UK

Abstract

Background: Children with Down syndrome (DS) are vulnerable to obstructive sleep apnea (OSA) due to their unique craniofacial anatomy and hypotonia. Understanding the predictors of OSA in DS may inform targeted screening.

Methods: 202 children with DS aged six months to sixth birthday (110 boys) were recruited from three UK children's hospitals. Clinical assessment included height, weight and tonsillar size. Parents set up cardiorespiratory polygraphy at home or chose laboratory studies. Studies with less than four hours of interpretable data were repeated where possible. AASM 2012 scoring criteria were used to derive an obstructive apnea/hypopnea index (OAHI). Predictors of moderate to severe OSA were examined.

Results: 188/202 (93%) participants were successfully studied. Of these, 169 studies were completed at home and 19 in a sleep laboratory. Moderate –severe OSA, defined by an $OAHI \geq 5$ /hour, was found in 14%; and mild-moderate OSA ($OAHI \geq 1 < 5$ /hr) in 59% of children. Male gender and habitual snoring predicted OSA but did not have independent predictive power in the presence of the other factors. Age in months, BMI centile and tonsillar size did not predict OSA.

Conclusions: Moderate to severe OSA is common in very young children with DS.

Examination of tonsillar size did not predict OSA severity. Population based screening for OSA is recommended in these children and domiciliary cardiorespiratory polygraphy offers an acceptable screening approach. Further research is needed to understand the natural history, associated morbidity, optimal screening methodology and treatment modality for OSA in these children.

Keywords (maximum 6)

1. Down Syndrome
2. Obstructive Sleep Apnea
3. Sleep Disordered Breathing
4. Cardiorespiratory polygraphy

Abbreviations

DS	Down syndrome
EEG	Electroencephalogram
EMG	Electromyogram
EOG	Electro-oculogram
OSA	Obstructive sleep apnea
OAHI	Obstructive sleep apnea/hypopnea index
ODI	Oxygen desaturation index
PSG	Polysomnography
PG	Polygraphy
SpO ₂	Oxyhemoglobin saturation
TD	Typically developing
TTA	Total time analysed

1. Background

Down syndrome (DS) is the leading genetic cause of childhood intellectual disability worldwide affecting between 1 in 650-1000 live births¹. Improved medical care means that children born this century are expected to live to middle age and beyond². Increased life-expectancy brings a welcome focus on quality of life.

An extensive literature in typically developing (TD) children indicates that untreated OSA is associated with reduced quality of life³, increased health care utilization⁴, impaired attention⁵, learning⁶ and school performance⁷. There is every reason to assume the same would apply to children with DS. Indeed, a recent study of 38 children with DS identified an association between OSA, reduced cognitive flexibility and lower Verbal IQ⁸. Indeed, it is arguable that children with DS may be at higher risk of cognitive impairment than TD children, as they have limited cognitive reserve to compensate for OSA-induced neural insult. Furthermore, untreated OSA could be a risk factor for later life Alzheimer's disease which affects 30% of adults with DS aged > 50 years⁹. Thus, timely recognition and treatment of OSA in these children is an important goal for optimal cognitive functioning and quality of life. Guidelines for screening for OSA in these children have been published in the UK¹⁰ and US¹¹. While these differ in their detail, both emphasise objective assessment of OSA with sleep studies before the age of 5 years and scheduled symptom enquiry in older children.

Children with DS have multiple risk factors for OSA. Hypotonia, obesity and craniofacial anatomy (small midface and macroglossia) all contribute to upper airway collapse in sleep. This is further exacerbated in the pre-school years by growth of the adenotonsillar tissue¹². Despite the evident risks of OSA in these children, over the past 25 years only eleven studies^{13,14,15,16,17,18,19,20,21,22,23} have reported the prevalence and correlates of OSA in a total of 489 children. Reported prevalence rates vary significantly, from 0 to 100%, reflecting the use of different, and often non-standard, scoring criteria for respiratory events, lack of agreement

as to what constitutes clinically relevant OSA and, in most, small sample size and/or wide age ranges.

Seven studies reported correlates of OSA and findings are contradictory. In the two largest studies to date, de Miguel-Diez and colleagues¹⁷ reported on 108 children aged 1-18 years and Maris and colleagues on 122 children aged 1-10.5 years. Both observed an inverse relationship between OSA and age. This was supported by Dyken¹⁵ et al in a study of 19 children aged 3-19 years, while conversely Ng et al reported the converse, namely a positive relationship between age and OSA in 22 children¹⁸. While de Miguel-Diez reported an association between OSA and male sex this was not supported by any other study. BMI would be predicted to be associated with OSA, and while two studies did report a positive association^{Error! Bookmark not defined.}¹⁸, five found none^{13, 20, 21, 22}. Both of the largest studies,^{17, 22} together reporting on 230 children, reported no association with tonsillar hyperplasia and one found no association with congenital heart disease¹⁷.

Thus while published guidelines recommend routine OSA screening in young children, there is a lack of reliable data on population prevalence in this group. We aimed to recruit a large cohort of young children with DS to determine the prevalence and predictors of OSA and to generate a research cohort for long term follow-up.

2. Methods

2.1 Setting: This study was conducted in three children's hospitals in the UK: Sheffield Children's Hospital in the North of England, Evelina London Children's Hospital, and Southampton Children's Hospital in the South of England.

2.2 Inclusion and exclusion criteria: Children were eligible for inclusion if they had a confirmed diagnosis of DS, were aged six months to sixth birthday and the family were prepared to travel to a recruiting centre. Exclusion criteria included: children screened for

OSA by cardiorespiratory study in the preceding 3 months; those receiving home oxygen therapy or non-invasive ventilation.

2.3 Recruitment: Children were recruited between July 2013 and January 2015 by multiple routes: firstly by local neurodevelopmental paediatricians who either approached families directly, or indirectly through posters in child developmental centres, secondly through specialist paediatricians within the Children's hospitals (cardiology, respiratory and neurology lists) and finally through advertising to local support groups, the UK Down Syndrome Association website and through word of mouth between parents.

2.4 Ethics committee approval: The study was approved by the UK National Research ethics committee (reference number: 13/SC/0106) and was adopted by the National Institute of Health Research portfolio (ID: 14250). Parents provided written consent on behalf of their child.

2.5 Measures:

2.5.1. Demographic and medical history: Parents completed a questionnaire detailing educational level of the primary carer and their child's relevant medical history including gestation at birth, history of adenoidectomy and/or tonsillectomy, rhinitis, asthma and congenital cardiac disease. Current snoring status was recorded based on response to the question: 'How often does your child snore when they do NOT have a cold?' with response options 'Never, rarely, occasionally, almost always, always, unknown'.

2.5.2 Clinical examination: Children were weighed and measured (length or height as appropriate to age) and DS-specific body mass index was computed from customized growth charts for children aged 2 years and over (Harlow publishing, UK). Where cooperation could be achieved, examination of the oropharynx was undertaken to grade tonsillar size using the Brodsky classification.

2.5.3 Domiciliary cardiorespiratory polygraphy (PG): OSA was assessed using the SOMNOtouch device (Somnomedics, Germany) comprising: chest and abdominal respiratory inductance plethysmography (RIP); pulse oximetry (Nonin) yielding oxyhemoglobin saturation (SpO₂), plethysmography and pulse signals; nasal pressure flow with integral snore sensor; body position sensor; and actigraphy. The lightweight (50g) headbox allowed the device to be body-worn in all participants. Following pilot testing in healthy volunteer children, the equipment was customized for the purpose of the study with both shortened nasal prongs and connecting leads between the chest and abdominal RIP bands. This minimised risk of accidental disconnection of equipment or entanglement.

2.5.4: Location of study and procedure: Children with DS are known to have restless sleep and compliance with sleep study sensors can be challenging. Parents were encouraged to attempt domiciliary PG studies to improve the child's chance of achieving the best quality sleep. However, where parents expressed a preference, or if home studies failed, children were studied, using identical equipment, in an attended sleep laboratory environment. For domiciliary studies parents were trained in equipment set up and use, and RIP bands were measured to fit the child. Step by step written instructions, supplemented by photographic images of equipment set-up, were provided, along with a telephone contact number, in case of difficulties. Domiciliary studies were performed the night after parent training and devices were returned the next day by courier.

2.6 Quality standards and scoring of sleep studies: A detailed standard operating procedure was generated. Studies were scored by an experienced technologist (RK), blinded to the clinical status of the child, using Domino Light software (Somnomedics, Germany). Every 10th study acquired was re-scored by a second experienced technologist (JG) who was blind to the original scoring. Similarly, the original scorer was not aware of which study was to be re-scored. Sleep and wake were systematically estimated for each 30 second epoch using a

combination of a parental sleep log to interpret sleep onset and offset, and the in-device actigraphy. Artefact was marked for RIP, oximetry and nasal flow signals independently. To comply with AASM scoring criteria, where 2 or more signals were poor quality, global artefact was marked and data excluded. Studies with less than 4 hours of interpretable data²⁴ were rejected and parents were given the option of repeating the study at home or in the sleep laboratory. Respiratory events were scored according to standard pediatric scoring criteria for adapted sensors²⁵. Specifically, obstructive apnea (OA) was scored when nasal pressure signal decreased to $>90\%$ amplitude of pre-event baseline for at least two breaths with ongoing inspiratory effort, and hypopnea where signal amplitude decreased by $> 30\%$ accompanied by a minimum of 3% oxyhemoglobin desaturation with ongoing inspiratory effort. Where nasal flow signal was lost, assuming that good quality RIP and oximetry signals were present, an 'undefined apnea' was scored, where RIP sum indicated paradoxical breathing in the presence of a minimum 3% oxyhemoglobin desaturation for at least 2 breaths. Respiratory events were scored as a mixed apnea when OA criteria were met for at least the duration of 2 breaths during baseline breathing, associated with absent respiratory effort during one portion of the event and the presence of inspiratory effort in another portion, regardless of which portion came first. Central apnea (CA) was scored where inspiratory effort was absent for at least the duration of two breaths and was associated with $\geq 3\%$ oxygen desaturation. In the absence of oxygen desaturation CA was also scored in children > 12 months of age where inspiratory effort was absent for 20 seconds or longer and < 12 months of age where the event lasted at least the duration of two breaths and was associated with a decrease in heart rate to < 50 beats per minute for at least 5 seconds or < 60 beats per minute for 15 seconds. Mean, minimum and 3% oxyhemoglobin desaturation index were automatically computed for total estimated sleep time. Total sleep time in minutes with high quality flow signal present was computed. The obstructive apnea/hypopnea index (OAHl)

was calculated by summing the obstructive apnea, hypopnea, mixed and undefined apnea indices.

2.7 Statistical analysis: Data were entered into SPSS v 22 (IBM). Prior to analysis all data were inspected for normality. Differences between centres were examined using ANOVA, Kruskal-Wallis or chi-squared statistics depending on the type of variable. Two group comparison used two-sample t-tests, Mann-Whitney U or chi-squared tests as appropriate. The distribution of OAH1, log transformed for ease of presentation, is displayed using a dotplot. Prevalence of OSA defined by OAH1 falling above previously suggested cut-point is expressed as a percentage with 95% confidence intervals (CI) calculated using CIA²⁶. Reliability coefficients were produced in SPSS with 95% CIs to assess inter-rater reliability. Logistic regression with dependent variable (OAH1 \geq 5) was carried out for selected predictors of OSA on their own and in the presence of other predictors to assess independent predictive power. Odds ratios are presented with 95% CIs and tested for significance using likelihood ratio tests.

3. Results

3.1 Recruitment (figure 1)

A total of 277 families were contacted by the recruitment sites and provided with information about the study. The multi-method recruitment approach was successful with 48% identified by their neurodevelopmental paediatrician, 21% by a tertiary specialist, 21% via websites and social media and 8% via personal recommendation from another participating parent. Data on method of identification of potential participants was missing for 8 cases. Recruitment rates were highest for eligible families referred by personal recommendation (90%); followed by neurodevelopmental paediatrician (79%); websites (66%) and tertiary paediatrician (61%). Of the 277 children identified, 266 (96%) met the eligibility criteria. Failure to meet the inclusion criteria included age (n=9) and use of home oxygen or non-invasive ventilation

therapy (n=2). Of the 266 remaining eligible children, families of 64 children (24%) decided not to participate; 19 did not give a reason (often failing to make further contact having received the study information); 10 cited factors relating to the child's health, for example, planned surgery or recent ill health; 32 cited family related factors, for example, distance to travel to the research center or demands of the study; 1 family reported a previous negative experience of a sleep study and 2 families gave other reasons. There were no differences in age or gender between the 202 eligible children who were successfully recruited to the study and the eligible children where families chose to not take part (median age 2.8 years, versus median age 3.0 years, (range in both cases 0.5-5.9 years), $P=0.54$) and 110 (54%) versus 37 (60%) boys respectively, $P=0.67$. Age was missing for 6 eligible children who were not recruited.

3.2 Demographic and clinical data

Demographic and clinical data are presented in table 1 for the 202 children recruited, both by recruitment site, and as a total across the entire study. There were no differences between the sites in age or gender profiles, gestation at birth of participants, nor in educational level of the primary carer. Almost one third of participants always, or almost always, snored in the absence of a cold. Of the 32 children who had a history of adenoidectomy and/or tonsillectomy; 4 had tonsillectomy alone and 3 had adenoidectomy alone. Mean age at surgery was 48 months (range 5-68 months). Children with a history of upper airway surgery were significantly older than those who had not had surgery (median age 53.0 months, range 31-71 months, versus 29.0 months, range 6-71 months; $P<0.0001$) but there were similar proportions who always or almost always snored in the absence of a cold (12/32 v 51/163, $P=0.358$). A history of rhinitis (n=46) and wheeze (n=96) was commonly reported. There were differences between sites with respect to children reported to wheeze ($P=0.000$) with a higher percentage at the Southampton site (68%) compared to London (40%) or Sheffield

(27%), although prophylactic inhaler use was similar across sites. There were also differences with respect to cigarette smoking in the home. Predictably, more of the children exposed to cigarette smoke were reported to wheeze compared to children who were not exposed (16/21, 76% versus 80/180, 44%, $P=0.006$). More children in Southampton were reported to have a congenital cardiac defect compared to the other sites. Cooperation with oro-pharyngeal examination was achieved in 88% of participants. There were no differences between sites in percentage of children with tonsillar hypertrophy (Brodsky grade 3-4). Children that were not examined were significantly younger than those who were successfully examined (median age 19 months versus 39 months (both range 6-71 months)). The majority of children were within a healthy BMI range, as may be predicted with a young population, with 19% of those aged 2 years and above classified as overweight or obese according to customised DS growth charts.

3.3 Cardiorespiratory polygraphy

Of the 202 consented children, one was excluded prior to PG as they commenced home oxygen and became ineligible, and one dropped out. Of the remaining 200 children, 194 families (97%) agreed to a domiciliary PG study. Families of 6 children chose to have studies in the sleep laboratory. Figure 2 illustrates the locations of PG studies, including those that were repeated (due to < 4 hours of interpretable data) as well as the points at which children dropped out. Overall, 188 successful studies were achieved requiring an average of 1.3 studies per successful data acquisition. Of the domiciliary PG studies, 74% were successful on first attempt compared to 95% of studies in the sleep laboratory.

3.4 Inter-rater scoring reliability

Blind inter-rater scoring was undertaken for 17 studies. A reliability coefficient of 0.917 (95% CI 0.791 to 0.969) was achieved for the main outcome variable, OAH1, and 0.988 (95% CI 0.967, 0.995) for estimated total sleep time (i.e. total time analysed, TTA), indicating

excellent inter-rater scoring agreement. Taking an OAHl threshold of $\geq 5/\text{hr}$ as a diagnostic criteria for moderate to severe OSA there was 100% agreement between the two scorers.

3.5 Quality of studies

Across the three centres children achieved on average just over 8 hours of TTA (mean 499.1, SD 101.6, range 261-673 minutes). Comparing the 19 studies achieved in the laboratory and the 169 achieved in the home setting, TTA was greater in home studies compared to laboratory studies but this difference was not statistically significant (median home 514 versus 468 minutes in laboratory, $P=0.170$). Similarly total time with flow in situ did not differ significantly between the two settings although was greater in the laboratory than at home (median home 212 versus 309 minutes in laboratory ($P=0.835$)). There was a weak positive correlation between age and TTA ($r = .18$, $P=0.012$), with older children achieving more minutes of artefact-free data, but not between age and total time achieved with flow in situ.

3.6 Respiratory variables

Table 2 illustrates the respiratory parameters derived from the scored cardiorespiratory PG studies. There were no differences by center, other than in total artefact free data analysed which was significantly higher in the Southampton and Sheffield centres compared to the London centre (median 537 mins and 498 respectively versus 469 mins; $P=0.004$). Figure 3 illustrates distribution of OAHl values across the entire group. As can be seen, the majority of children, 73%, (95% CI 66%-79%), have an OAHl $\geq 1/\text{hour}$, that indicates at least mild OSA. Given the lack of certainty about what constitutes a clinically significant OAHl in children with DS, the data are also presented according to different diagnostic thresholds

(table 3). Importantly, even taking a more conservative threshold of OAH_I \geq 5/hour, we report prevalence rates of 14% (95% CI 10%, 20%).

3.7 Factors predicting OSA

Key potential predictors of moderate-severe OSA, as defined by an OAH_I of $>$ 5/hour, were examined (table 4). Age, parental socio-economic status, gestation at birth, exposure to cigarette smoke in the home, history of wheeze, rhinitis and congenital cardiac disease, overweight and obesity did not predict OSA. The prevalence of severe OSA was slightly higher (6; 21%) amongst the 29 children with previous tonsillectomy and/or adenoidectomy than amongst the 147 children without this history (19; 13%) but the difference was not statistically significant (P=0.274). In the unadjusted model male gender and clinical history of ‘always or almost always snoring in the absence of a cold’ predicted OSA but did not have independent predictive power in the presence of the other factors.

Discussion

This is the largest study reported to date describing the prevalence and predictors of OSA in a young, European population of children with DS. We have reported OSA prevalence based on multiple diagnostic thresholds as a reference point for future research.

Large population based studies in TD children have established that moderate to severe OSA (OAH_I of \geq 5/hour) is associated with risk of systemic hypertension²⁷ and a broad range of neuropsychological impairments²⁸. Importantly, a recent European Respiratory Society task force²⁹ concluded that an OAH_I \geq 5 per hour was a meaningful clinical treatment threshold in TD children aged 2-18 years, irrespective of symptomatology. We report a prevalence rate of 14% (95% confidence intervals 10-20%) of moderate to severe OSA in our sample, higher than the 0.2% prevalence reported in healthy TD 5-7 year olds²⁷, but lower than previous reports in children with DS. De Miguel-Diez and colleagues¹⁷, reported moderate to severe OSA in 45% of 108 children aged 1-18 years, while Austeng et al. reported a 66% prevalence

in 25 children aged 8 years²¹. A number of factors may explain the lower prevalence in our study group. Firstly our population was considerably younger than in previous studies, with a narrow age range. While de Miguel-Diez et al. reported a small but positive association between younger age (< 8 years) and OSA¹⁷, a large population-based study of 700 TD children reported lower prevalence rates of OSA in children aged 5-7 years (0.2%) compared to children aged 9-12 years (2.0%)²⁷. Maris et al²² reported OSA in 66.4% of 122 children with DS aged 0-18 years (based on a threshold of OAH_I ≥ 2/hour), this compares to 44% at this diagnostic threshold in our study. However, the two populations cannot be directly compared. In contrast to our data, 57% of Maris's sample were clinically referred due to concerns about sleep disordered breathing. However, considering only the children over 4 years of age, (who were routinely screened for OSA), a lower prevalence of OSA (53.8%) was reported, closer to our prevalence data of 44%.

Finally, there may have been differences in the prevalence of overweight/obesity between our population and previous studies, although comparisons are constrained by the use of non-standardised BMI data in previous reports rather than age and gender, DS specific BMI centiles used here.

Future work is needed in a large sample of children with DS to establish the OSA severity thresholds associated with increased risk of neurocognitive and cardiovascular morbidity. We hypothesise that these children may be more vulnerable than TD children to the additional burden of OSA given their limited cognitive reserve and increased prevalence of congenital cardiac abnormalities. However, given the poverty of literature on OSA-associated morbidity in children with DS, and the increased risks associated with surgery³⁰, few clinicians would recommend adenotonsillectomy at lower OAH_I thresholds in the absence of clear OSA associated morbidity. We therefore focused our analysis of predictors of OSA using a diagnostic threshold of an OAH_I ≥ 5/hour. Unlike recent findings in a large community

sample of TD children²⁷, our data suggested male gender to be a risk factor for OSA but predictive power was reduced after controlling for other variables. In line with the findings of de Miguel-Diez we did not demonstrate that body mass index centile (albeit using more specific DS growth charts), tonsillar grading or history of congenital cardiac abnormality predicted OSA. Data from a large cohort of TD children suggest that waist circumference, rather than BMI, may be a better predictor of OSA²⁷ and this could usefully be assessed in future studies. A history of regular snoring (always or almost always) was reported in almost one third of children, this compares to 3.6-7.7% of TD young children aged 6 months to 6.75 years in a large UK population³¹. On its own this factor was associated with over twofold increase in risk of OSA, but it did not have statistically significant independent predictive power in the presence of other factors. Previous researchers have reported clinical history and tonsillar grading to be poor predictors of OSA^{32,33}. Finally, we report for the first time in this population, that parental educational level, gestation at birth, exposure to cigarette smoke in the home and history of wheeze, and rhinitis are not major predictors of OSA.

Study limitations

It is important to recognise the limitations of the measurement technique chosen. The American Academy of Sleep Medicine³⁴ recommends full polysomnography (PSG) for the investigation of childhood OSA, although recognises cardiorespiratory PG as a reliable alternative in adults.³⁵ Like de Miguel-Diez and colleagues¹⁷, we chose to use domiciliary cardiorespiratory PG rather than laboratory PSG in this population. The choice was influenced by a number of factors; importantly, public consultation during protocol development indicated that parents were enthusiastic to trial home studies and many cited prior experience of their child sleeping poorly in a hospital setting. This was born out by the high uptake rate of domiciliary studies (94%) achieved in this study. In much of mainland Europe, full PSG is not available and the European Respiratory Society taskforce recognises

PG as an alternative diagnostic tool when PSG is not *'fiscally or practically'* viable²⁹.

Cardiorespiratory PG can be used in the home setting where children, particularly those with learning disabilities, may sleep better than in hospital³⁶. The principle limitation of PG is underestimation of the OAHl, as this technique cannot detect hypopneas associated with arousal rather than oxygen desaturation. Furthermore, in the absence of neurophysiological measures of sleep, interpretation of the sleep-wake state is constrained. The experienced scorers in this study achieved remarkable agreement in their scoring of total sleep time based on available signals and found the integrated actigraphy helpful in this respect. In support of this technology choice, recent data demonstrated that domiciliary PG predicted OSA (defined by OAHl ≥ 5.6 /h on full PSG) with a sensitivity of 90.9% (95% CI, 79.6%-100%) and a specificity of 94.1% (95% CI, 80%-100%)³⁷. Nonetheless it is possible that PG will have underestimated the OAHl in this population, particularly at lower diagnostic thresholds. We assessed the accuracy of cardiorespiratory PG compared to full PSG using the Somnotouch device with an added sleep module (standard EEG.EMG/EOG electrodes) in two children. The first was a 9 year old healthy volunteer studied at home and the second was a 7 year old inpatient with possible OSA. Neither study was attended. Two copies of the studies were made. The first was scored without sleep signals and the second scored with full polysomnography channels and sleep staging. OAHls measured by PSG versus PG were not clinically significantly different (case 1: 0.2 v 0.1/hr; case 2: 6.6 v 6.1/hr respectively). Future evaluation of the accuracy of cardiorespiratory PG versus full PSG using this device in children with Down syndrome would be of value.

A further limitation was the choice to not measure carbon dioxide overnight, so that we could not assess hypoventilation in these children. This was a pragmatic decision. Our aim was to assess obstructive events and we were concerned to streamline sensors to achieve optimal core signals.

Selection bias was limited through using multiple recruitment routes, the majority of children were recruited either from routine neurodevelopmental follow-up or through parent support networks. The fact that more children with congenital heart disease were recruited from the Southampton site, indicates a potential sampling bias in this centre. However, the presence of congenital heart disease was not one of the greatest predictors of OSA in our study, so it is unlikely this resulted in systematic bias in the prevalence of OSA reported. Furthermore our overall prevalence (69%) of parent reported congenital heart disease (which included temporary defects such as patent ductus arteriosus) was only slightly greater than estimates of population prevalence of up to 60% previously reported³⁸.

4. Conclusions and future work

In summary, we report moderate to severe obstructive sleep apnea in 14% of a large cohort of 188 young children with DS. This was not predicted by age, tonsillar size or body mass index standardised centile. On the basis of these findings we recommend that young children with DS are routinely screened for OSA in their pre-school years using objective measures, as clinical evaluation alone may be misleading. Further work is needed to identify the optimum method of screening, taking into account practical clinical challenges in children with intellectual disabilities. Our experience suggests that domiciliary cardiorespiratory studies are acceptable to many families. Importantly, fundamental knowledge needs to be built about the natural history, associated morbidity and optimum treatment approaches in this population, where OSA is likely to be associated with greater morbidity. The paucity of research in this field does not reflect a lack of health need, rather the invisibility of children with developmental disorders in mainstream pediatric research³⁹. Children with DS are readily identifiable within health services and, from our experience, parents are enthusiastic for their child to participate in research. This research imbalance needs to be urgently and assertively

addressed. It cannot be assumed that OSA research in TD populations translates to children with DS who have different anatomical risk factors and cognitive profiles.

Figure 1: Recruitment

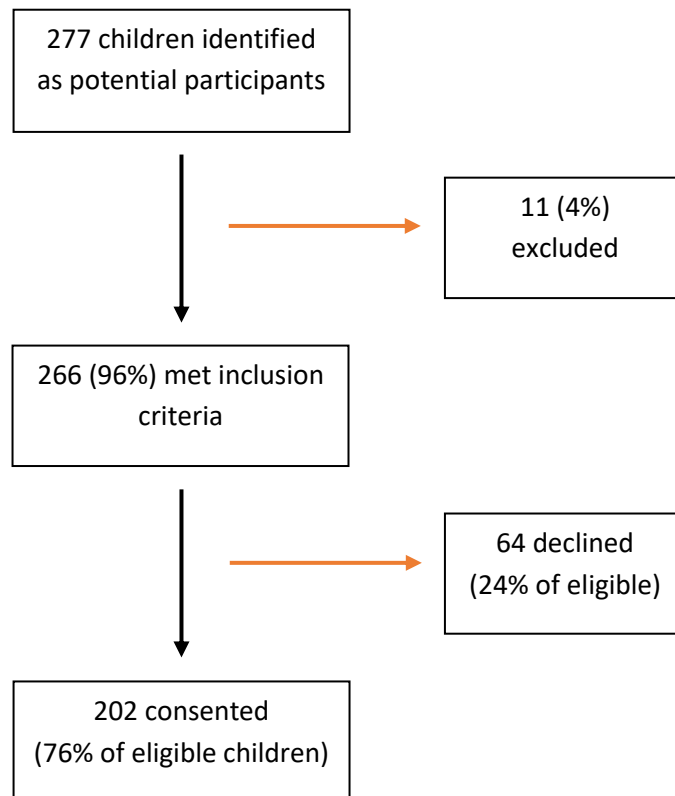


Figure 2: Setting for cardiorespiratory studies

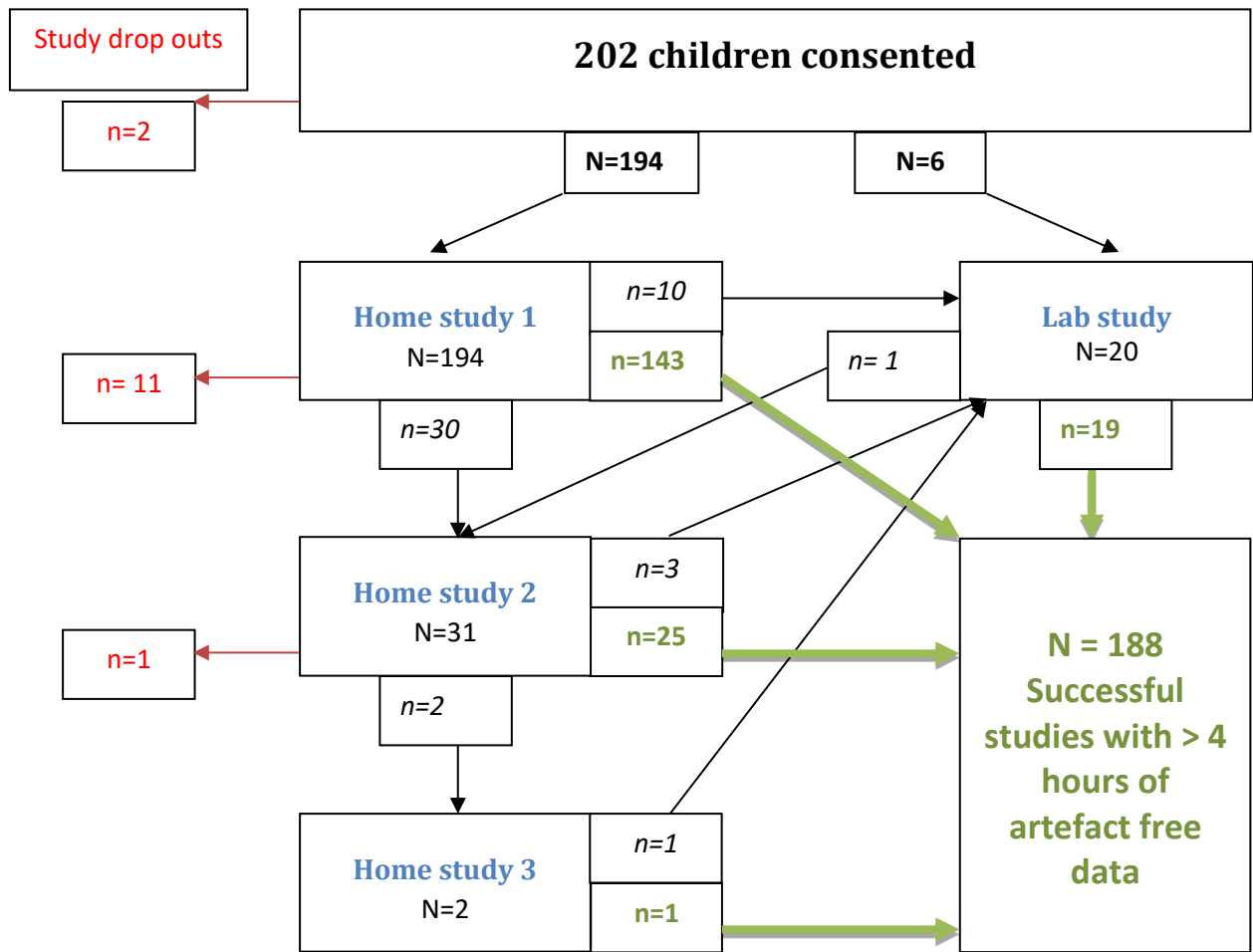


Figure 2 legend: Flow of participants through cardiorespiratory studies illustrating success rates and numbers repeated in each setting. Numbers in red indicate where children dropped out of study having failed to achieve an adequate cardiorespiratory study, those in black indicate children who had repeat studies and those in green indicate successful studies.

Table 1: Demographic and clinical characteristics of participants from each centre. Figures are number (%) unless stated otherwise.

		S'hampton	London	Sheffield	All centres	P value
Maximum numbers available¹		82	60	60	202¹	
Male gender		40 (49%)	33 (55%)	36 (62%)	110 (55%)	0.312 ²
Age in months	mean (min to max)	38 (6 to 71)	35 (6 to 71)	35 (6 to 71)	36 (6 to 71)	0.511 ³
Education of primary carer	Degree or higher HND⁷ or equivalent	33 (42%)	27 (45%)	21 (37%)	81 (42%)	0.097 ⁴
	A-level	21 (27%)	13 (22%)	3 (5%)	37 (19%)	
	GCSE⁸ A-C grade \geq 1	8 (10%)	5 (8%)	12 (21%)	25 (13%)	
	Lower grade GCSE or below	9 (12%)	10 (17%)	11 (19%)	30 (15%)	
Gestation (WHO category)	Term (\geq37)	7	5	10	22	0.501 ⁴
	Moderately preterm (32-36)	61 (74%)	47 (80%)	46 (78%)	154 (77%)	
	Very preterm (28-31)	18 (22%)	11 (19%)	13 (22%)	42 (21%)	
	Extremely preterm (<28)	1	1	0	2	
Does the child always or almost always snore when they do not have a cold		2	0	0	2	0.170 ²
History of tonsillectomy and/or adenoidectomy		22 (28%)	24 (42%)	17 (29%)	63 (32%)	0.170 ²
History of rhinitis		14 (17%)	9 (15%)	10 (17%)	33 (16%)	0.944 ²
History of wheeze		24 (30%)	15 (26%)	7 (12%)	46 (23%)	0.037 ²
Use of prophylactic inhalers for wheeze		56 (69%)	24 (40%)	16 (27%)	96 (48%)	0.000 ²
Cigarette smoker in the home		9 (11%)	11(18%)	7 (12%)	27 (13%)	0.451 ²
Congenital cardiac defect		14 (17%)	3 (5%)	4 (7%)	21 (10%)	0.035 ²
Brodsky grading⁵ (% of those examined)	Grade 0-2 (or tonsils removed)	67 (82%)	35 (58%)	37 (62%)	139 (69%)	0.004 ²
	Grade 3-4	45 (76%)	36 (75%)	30 (60%)	111 (71%)	
	Uncooperative (%total)	14 (24%)	12 (25%)	20 (40%)	46 (29%)	
BMI centile (restricted to those aged \geq 2 years, omitting uncooperative from %s)	Underweight	23 (28%)	12 (20%)	10 (17%)	45 (22%)	0.430 ⁴
	Normal weight	2 (4%)	2 (5%)	1 (3%)	5 (4%)	
	Overweight	43(77%)	32 (82%)	25 (74%)	100 (78%)	
	Obese	3 (5%)	2 (5%)	2 (6%)	7 (5%)	
	Uncooperative	8 (14%)	3 (8%)	6 (18%)	17 (13%)	
Overweight/obese (restricted to those aged \geq 2 years,		3	1	1	5	0.485 ⁶

1 7 missing values for education level and snoring; 3 missing values for rhinitis; 2 missing values for gestational age; 1 missing value for wheeze

2 Chi-squared test for differences across centers

3 ANOVA for differences.3 in means across centers

4 Kruskal-Wallis test for differences across centers

5 Grade 0-2 occupy 0-50%, and grade 3-4 occupy 50-100% of the space between the tonsillar pillars

6 Percentages and chi-squared test for difference across centers excluding uncooperative children

7 HND (Higher National Diploma) UK qualification used for university entrance at advanced level, in some circumstance considered equivalent to the second year of a three-year university degree course.

8 GCSE (General Certificate of Secondary Education) state examination for children aged 16 years.

Table 2: Distribution of Apnea/Hypopnea indices

Successful studies number = 188	Median	IQR	Min to max
Artefact-free analysis time (mins)	506name	423.5 to 584.8	261 to 673
Mean oxyhemoglobin saturation %	98	97 to 99	88 to 100
Min oxyhemoglobin saturation %	88.0	83 to 90	39 to 97
3% oxygen desaturation index	12.4	7.2 to 22.0	0.2 to 106.6
Obstructive apnea index	0.2	0.0 to 0.9	0.0 to 48.3
Obstructive hypopnea index	0.2	0.0 to 1.0	0.0 to 14.5
Central apnea index	1.7	0.9 to 3.1	0.0 to 14.7
Mixed apnea index	0.0	0.0 to 0.1	0 to 1.8
Undefined apnea index	0.6	0.1 to 1.4	0.0 to 57.3
Obstructive apnea/hypopnea index	1.7	0.9 to 3.2	0.0 to 110.4

Table 3: Prevalence of OSA based on suggested OAHl thresholds

Diagnostic OAHl threshold	n	Prevalence (95% CI)
≥ 10/hour	15/188	8% (5%, 13%)
≥ 5/hour	27/188	14% (10%, 20%)
≥ 2/hour	82/188	44% (37%, 51%)
≥ 1.5/hour	110/188	59% (51%, 65%)
≥ 1/hour	138/188	73% (67%, 79%)

Table 4: Predictors of OAHI \geq 5/hour

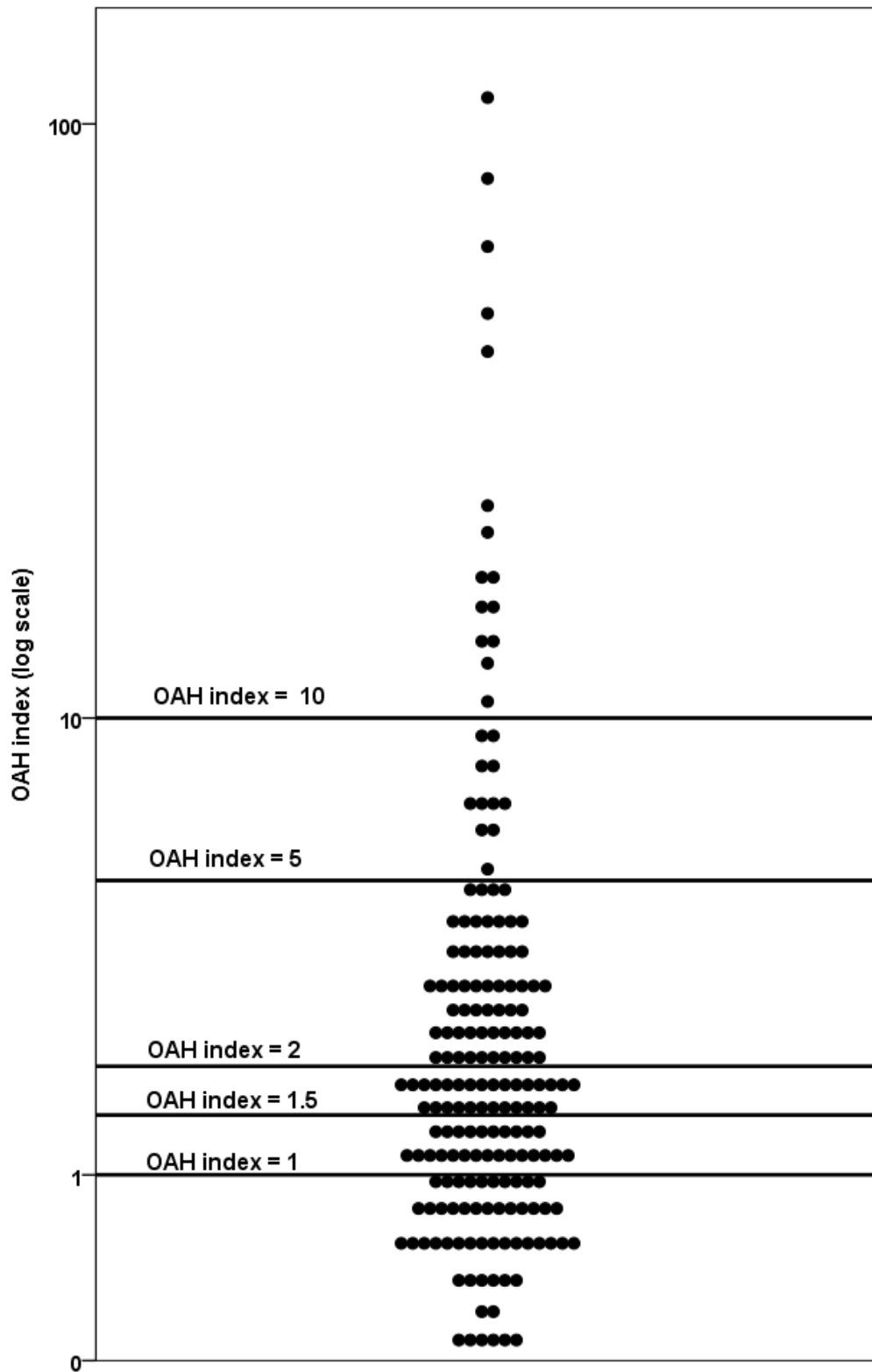
	Unadjusted (n=176 ¹)		Adjusted ² (n=176)	
	Odds ratio ² (95% CI)	P	Odds ratio ⁴ (95% CI)	P
Male (vs female) gender	2.68 (1.06, 6.78)	0.030	2.55 (0.96, 6.79)	0.053
Age per unit increase in months	0.99 (0.97, 1.01)	0.482	0.98 (0.96, 1.01)	0.200
Parents' educational level per one category increase	0.87 (0.66, 1.13)	0.290	0.90 (0.66, 1.22)	0.503
Gestational per unit increase in weeks	1.06 (0.88, 1.27)	0.552	1.03 ((0.84, 1.27)	0.754
Cigarette smoker in the home	0.31 (0.04, 2.42)	0.188	0.22 (0.03, 1.87)	0.100
History of tonsillectomy and/or adenoidectomy	1.76 (0.63, 4.87)	0.294	2.48 (0.74, 8.35)	0.149
History of rhinitis	1.29 (0.50, 3.34)	0.606	0.99 (0.33, 2.99)	0.984
History of wheeze	2.00 (0.83, 4.82)	0.114	1.85 (0.71, 4.81)	0.204
Congenital cardiac defect	0.78 (0.32, 1.89)	0.584	0.82 (0.31, 2.17)	0.697
Child always or almost always snore when they do not have a cold	2.40 (1.02, 5.65)	0.046	1.97 (0.73, 5.35)	0.183
Brodsky grade per unit increase in grade (n=140)	0.95 (0.61, 1.48)	0.818	0.53 (0.27, 1.04)	0.054
Overweight/obese restricted to those aged \geq 2 years (n=114)	0.69 (0.14, 3.34)	0.635	0.72 (0.10, 5.16)	0.645

¹ 176 children with complete information on OAHI and the predictors listed²

² Adjusted for gender, age, educational level, gestational age, smoking, history of tonsillectomy/adenoidectomy, rhinitis, wheeze, cardiac defect, snoring without a cold

³Odds ratios less than 1 indicate that the predictor reduces the odds of OAHI \geq 5/hour. Odds ratios greater than 1 indicate that the predictor increases the odds of OAHI \geq 5/hour

Figure 2: Distribution of the OAHI showing potential diagnostic thresholds⁶



⁶ Note individual with OAHI = 0 has been included by replacing their value with the minimum 0.06

Acknowledgements

We would like to thank the UK Down Syndrome Medical Interest group as well as the Down Syndrome Association for their help with recruiting children to the study and most importantly the families who participated for their enthusiasm. We are also grateful to Dr Richard Tomlinson and his research nursing team at the Royal Devon and Exeter NHS Foundation Trust for their support as a satellite recruitment site.

Funding

This work was supported by Action Medical Research and the Garfield Weston Foundation [grant reference 2040].

References

- ¹ Stoll C, Alembik Y, Dott B, Roth MP. (1998) Study of Down syndrome in 238,942 consecutive births. *Ann Genet* 41: 44–51.
- ² Bittles AH and Glasson EJ. Clinical, social, and ethical implications of changing life expectancy in Down syndrome. *Dev Med Child Neurol*. 2004; 46 (.4): 282–286.
- ³ Mitchell RB, Kelly J. Behavior, neurocognition and quality-of-life in children with sleep-disordered breathing. *Int J Pediatr Otorhinolaryngol*. 2006; 70 (3):395-406.
- ⁴ Tarasiuk A, Greenberg-Dotan S, Simon-Tuval T, Freidman B, Goldbart AD, Tal A, et al. Elevated morbidity and health care use in children with obstructive sleep apnea syndrome. *Am J Respir Crit Care Med*. 2007; 175:55-61.
- ⁵ Khierandish L, Gozal D. Neurocognitive dysfunction in children with sleep disorders. *Dev Sci* 2006; 9(4):388–99.
- ⁶ Hill CM, Hogan AM, Karmiloff-Smith A. To sleep perchance to enhance learning– the importance of sleep to healthy neurodevelopment. *Archives of Disease in Childhood*. 2007; 92 (7) : 637–643.
- ⁷ Gozal D. Sleep-disordered breathing and school performance in children. *Pediatrics* 1998;102(3 Pt 1):616–20.
- ⁸ Breslin J, Spanò G, Bootzin R, Anand P, Nadel L, Edgin J. Obstructive sleep apnea syndrome and cognition in Down syndrome. *Dev Med Child Neurol*. 2014;56(7):657-64.
- ⁹ Fernandez F & Edgin JO. Poor Sleep as a Precursor to Cognitive Decline in Down syndrome: A Hypothesis. *Alzheimers Dis Parkinsonism*. 2013 26; 3(2): 124.
- ¹⁰ Royal College of Paediatrics and Child Health. Working Party on Sleep Physiology and Respiratory Control Disorders in Childhood, Standards for Services for Children with Disorders of Sleep Physiology Report. (2009).
- ¹¹ Marilyn J. Bull, the Committee on Genetics Health Supervision for Children with Down syndrome. *Pediatrics*. 2011, 128 (2) 393-406; DOI: 10.1542/peds.2011-1605.
- ¹² Marcus CL. Sleep-disordered Breathing in Children. *Am J Respir Crit Care Med*. 2001;164:16-30.
- ¹³ Marcus C, Keens T, Bautista D, et al. Obstructive sleep apnea in children with Down syndrome. *Pediatrics*. 1991;88:132.
- ¹⁴ Levanon A, Tarasiuk A, Tal A. Sleep characteristics in children with Down syndrome. *Journal of Pediatrics*. 1999; 134 (6): 755-760.

-
- ¹⁵ Dyken ME, Lin-Dyken DC, Poulton S, Zimmerman MB, Sedars E. Prospective polysomnographic analysis of obstructive sleep apnea in Down syndrome. *Arch Pediatr Adol Med.* 2003;157(7):655-60.
- ¹⁶ Dahlqvist A, Rask E, Rosenqvist CJ, Sahlin C, Franklin KA. Sleep apnea and Down's syndrome. *Acta Oto-Laryngologica.* 2003 Dec;123(9):1094-7.
- ¹⁷ de Miguel-Diez J, Villa-Asensi JR, Alvarez-Sala JL. Prevalence of sleep-disordered breathing in children with Down syndrome: polygraphic findings in 108 children. *Sleep.* 2003; 26(8):1006-9.
- ¹⁸ Ng D K, Hui H N, Chan C H, Kwok K L, Chow P Y, Cheung J M, Leung S Y. Obstructive sleep apnoea in children with Down syndrome. *Singapore Med J* 2006; 47(9) : 774-779.
- ¹⁹ Shott SR, Amin R, Chini B, Heubi C, Hotze S, Akers R. Obstructive sleep apnea: Should all children with Down syndrome be tested? *Arch Otolaryngol Head Neck Surg.* 2006;132(4):432-6.
- ²⁰ Fitzgerald DA, Paul A, Richmond C. Severity of obstructive apnoea in children with Down syndrome who snore. *Arch Dis Child* 2007;92:423–425
- ²¹ Austeng ME, Øverland B, Kværner KJ, Andersson EM, Axelsson S, Abdelnoor M, Akre H. Obstructive sleep apnea in younger school children with Down syndrome. *Int J Pediatr Otorhinolaryngol.* 2014;78(7):1026-9.
- ²² Maris M, Verhulst S, Wojciechowski M, Van de Heyning P, Boudewyns A. Prevalence of Obstructive Sleep Apnea in Children with Down Syndrome. *Sleep.* 2016 Mar 1;39(3):699-704. doi: 0.5665/sleep.5554.
- ²³ Lin SC, Davey MJ, Horne RS, Nixon GM. Screening for obstructive sleep apnea in children with Down syndrome. *J Pediatr.* 2014;165(1):117-22. doi: 10.1016/j.jpeds.2014.02.032.
- ²⁴ Urschitz MS, Brockmann PE, Schlaud M, Poets CF. Population prevalence of obstructive sleep apnoea in a community of German third graders. *Eur Respir J.* 2010;36(3):556-68.
- ²⁵ Berry RB, Budhiraja R, Gottlieb DJ, Gozal D, Iber C, Kapur VK, Marcus CL, Mehra R, Parthasarathy S, Quan SF, Redline S, Strohl KP, Davidson Ward SL, Tangredi MM; American Academy of Sleep Medicine. Rules for scoring respiratory events in sleep: update of the 2007 AASM Manual for the Scoring of Sleep and Associated Events. Deliberations of the Sleep Apnea Definitions Task Force of the American Academy of Sleep Medicine. *J. Clin Sleep Med.* 2012;8(5):597-619.
- ²⁶ Altman DG, Machin D, Bryant TN, Gardner MJ. *Statistics with Confidence* 2nd Ed. London BMJ Books; 2000.

-
- ²⁷ Bixler EO, Vgontzas AN, Lin H, Liao D, Calhoun S, Vela-Bueno A, Fedok F, Vukmir V, Graff G. Sleep Disordered Breathing in Children in a General Population Sample: Prevalence and Risk Factors. *Sleep*. 2009; 32(6): 731–736.
- ²⁸ Hunter SJ, Gozal D, Smith DL, Philby MF, Kaylegian J, Kheirandish-Gozal L. Effect of Sleep-Disordered Breathing Severity on Cognitive Performance Measures in a Large Community Cohort of Young School-Aged Children. *Am J Respir Crit Care Med*. Online 01 Mar 2016. DOI: 10.1164/rccm.201510-2099OC
- ²⁹ Kaditis AG, Alonso Alvarez ML, Boudewyns A, Alexopoulos EI, Ersu R, Joosten K, Larramona H, Miano S, Narang I, Trang H, Tsaoussoglou M, Vandebussche N, Villa MP, Van Waardenburg D, Weber S, Verhulst S. Obstructive sleep disordered breathing in 2- to 18-year-old children: diagnosis and management. *Eur Respir J*. 2016; 47(1):69-94.
- ³⁰ Tweedie DJ, Bajaj Y, Ifeicho SN, Jonas NE, Jephson CG, Cochrane LA, Hartley BE, Albert DM, Wyatt ME. Peri-operative complications after adenotonsillectomy in a UK pediatric tertiary referral centre. *Int J Pediatr Otorhinolaryngol*. 2012;76(6):809-15.
- ³¹ Bonuck KA, Chervin RD, Cole TJ, Emond A, Henderson J, Xu L, Freeman. Prevalence and persistence of sleep disordered breathing symptoms in young children: a 6-year population-based cohort study. *Sleep*. 2011;34(7):875-84.
- ³² Ng DK, Chan CH, Cheung JM. Children with Down syndrome and OSA do not necessarily snore. *Arch Dis Child*. 2007; 92(11):1047-8.
- ³³ Sproson EL, Hogan AM, Hill CM. Accuracy of clinical assessment of paediatric obstructive sleep apnoea in two English centres. *J Laryngol Otol*. 2009; 22:1-8.
- ³⁴ American Academy of Sleep Medicine. International Classification of Sleep Disorders. 3rd Edition Westchester, IL, American Academy of Sleep Medicine, 2014.
- ³⁵ Aurora RN, Zak RS, Karippot A, Lamm CI, Morgenthaler TI et al. Practice Parameters for the Respiratory Indications for Polysomnography in Children. *Sleep*. 2011; 34(3): 379–388.
- ³⁶ Das S, Mindell J, Millet GC, Ofer D, Beck SE, Mason T, Brooks LJ, Traylor J, Marcus CL. Pediatric Polysomnography: The Patient and Family Perspective. *J Clin Sleep Med*. 2011; 7(1): 81–87
- ³⁷ Reliability of Home Respiratory Polygraphy for the Diagnosis of Sleep Apnea in Children. Alonso-Álvarez ML, Terán-Santos J, Ordax Carbajo E, Aurelio Cordero-Guevara J, Navazo-Egüia AI, Kheirandish-Gozal L, Gozal D. *Chest*. 2015;147(4):1020-1028
- ³⁸ Torfs CP, Christianson RE. Anomalies in Down syndrome individuals in a large population-based registry. *Am J Med Genet*. 1998;77(5):431-8.
- ³⁹ Feldman MA, Battin SM, Shaw OA, Luckasson R. Inclusion of children with disabilities in mainstream child development research *Disability & Society*; 2013;28 (7): 997-1011.

