### Home oximetry to screen for obstructive sleep apnoea in Down syndrome

Catherine M. Hill[[1]](#footnote-1),[[2]](#footnote-2), Heather E. Elphick3,Michael Farquhar4, Paul Gringras4, Ruth M. Pickering1, Ruth Kingshott[[3]](#footnote-3), Jane Martin5, Janine Reynolds3, Anna Joyce[[4]](#footnote-4), Johanna C. Gavlak2, Hazel J. Evans2

***Corresponding author.***

Dr Catherine Mary Hill. BM MSc PhD 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](mailto:cmh2@soton.ac.uk)

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### Abbreviations

AF Artefact-free

AUC Area under the curve

CI Confidence interval

DS Down syndrome

NIHR National Institute for Health Research

OSA Obstructive sleep apnoea

OAHI Obstructive sleep apnoea/hypopnoea index

ODI Oxygen desaturation index

ROC Receiver Operating Characteristic

SpO2 Oxyhaemoglobin saturation

TD Typically developing

TTA Total time analysed

# ABSTRACT

### Objective: Children with Down syndrome are at high risk of obstructive sleep apnoea (OSA) and screening is recommended. Diagnosis of OSA should be confirmed with multi-channel sleep studies. We aimed to determine whether home pulse oximetry (HPO) discriminates children at high risk of OSA who need further diagnostic multi-channel sleep studies.

### Design: Cross sectional prospective study in a training sample recruited through three UK centres. Validation sample used single centre retrospective analysis of clinical data.

### Patients: Children with Down syndrome aged 0.5–6 years.

### Intervention: Diagnostic multi-channel sleep study and HPO

### Main outcome measures: Sensitivity and specificity of HPO to predict moderate to severe OSA.

### Results: 161/202 children with Down syndrome met quality criteria for inclusion and 25 had OSA. In this training sample, the best HPO parameter predictors of OSA were the delta 12s index >0.555 (sensitivity 92%, specificity 65%) and 3% oxyhaemoglobin (SpO2) desaturation index (3%ODI) >6.15 dips/hour (sensitivity 92%, specificity 63%). Combining variables (delta 12s index, 3% ODI, mean & minimum SpO2)achieved sensitivity of 96% but reduced specificity to 52%. All predictors retained or improved sensitivity in a clinical validation sample of 50 children with variable loss of specificity, best overall was the delta 12s index, a measure of baseline SpO2 variability (sensitivity 92%; specificity 63%).

### Conclusions: HPO screening could halve the number of children with Down syndrome needing multi-channel sleep studies and reduce the burden on children, families and health services alike. This approach offers a practical universal screening approach for OSA in Down syndrome that is accessible to the non-specialist paediatrician.

# What is already known on this topic

1. Obstructive sleep apnoea is common in Down syndrome, clinical diagnosis is unreliable and universal screening is recommended
2. Obstructive sleep apnoea can only be reliably diagnosed using multi-channel sleep studies which are expensive, demanding for families and only available in specialist centres
3. Initial screening with pulse oximetry could reduce the number of children needing diagnostic multi-channel studies but abnormal oximetry thresholds have not been determined

# What this study adds

1. Simple numeric oximetry parameters can sensitively detect most children at risk of clinically significant obstructive sleep apnoea
2. Universal oximetry screening is widely available and could halve the number of children needing confirmatory multi-channel sleep studies at specialist centres
3. The use of a simple screening threshold (the delta 12 second index) offers a screening approach that is accessible to the non-specialist paediatrician.

### INTRODUCTION

Down syndrome (DS) affects 1 in 1000-1100 live births a year worldwide. Obstructive sleep apnoea (OSA), which occurs in around 58% of these children[[5]](#endnote-1),[[6]](#endnote-2),[[7]](#endnote-3),[[8]](#endnote-4),[[9]](#endnote-5), can impair school performance[[10]](#endnote-6), behaviour [[11]](#endnote-7),[[12]](#endnote-8),quality of life[[13]](#endnote-9) and increase health care use[[14]](#endnote-10).

Screening for OSA is recommended as clinical evaluation is unreliable[[15]](#endnote-11),[[16]](#endnote-12),[[17]](#endnote-13),[[18]](#endnote-14),[[19]](#endnote-15) and, importantly, treatment options are available. The American Academy of Pediatrics recommends diagnostic polysomnography prior to school entry[[20]](#endnote-16) but this is poorly tolerated in these children[[21]](#endnote-17) and not universally available. A UK consensus group recommended5 annual screening with pulse oximetry to age 6 years followed by confirmatory diagnostic multi-channel sleep studies (polysomnography[[22]](#endnote-18) or cardiorespiratory polygraphy[[23]](#endnote-19)) for abnormal oximetry studies. Multi-channel sleep studies are important to identify central apnoea as an alternative cause of oxyhaemoglobin desaturation, hypoventilation and to assess the severity of OSA. Simple, automatically generated oximetry parameter thresholds have potential for universal screening and have been defined in adults[[24]](#endnote-20) but not yet in children. A decade after UK recommendations were made, there are no screening guidelines for OSA in DS children[[25]](#endnote-21),[[26]](#endnote-22).

We aimed to

1. Identify home pulse oximetry (HPO) parameters that sensitively detect children at risk of OSA, therefore needing diagnostic multi-channel studies, using research participants (training data-set)
2. Test how well these HPO parameters performed in a clinical setting (validation data-set)
3. Generate practical recommendations for OSA screening in DS children.

### METHODS

**Training data-set**

*Inclusion and exclusion criteria:* Eligible children had DS, were aged 6 months to six years. A history of ENT surgery was permitted. Children receiving home oxygen or non-invasive ventilation therapy were excluded.

*Setting:* Study sites included Sheffield, Evelina London and Southampton Children’s hospitals, UK.

*Ethics committee approval:* The study was approved by the UK National Research Ethics Committee (ID:13/SC/0106) and registered on the NIHR portfolio (ID:14250). Parents provided written consent.

*Recruitment**:* Children were recruited through multiple routes including via local neurodevelopmental paediatricians; specialist paediatricians within the Children’s hospitals and, finally, through advertising to local support groups, the UK Down Syndrome Association website and word of mouth between parents[[27]](#endnote-23). This multiple method approach aimed to minimise selection bias.

*Measures*

*Demographic and medical history*: parents reported their child’s medical history and snoring status.

*Clinical examination*: Children were weighed and measured and DS-specific body mass index was computed for children >2y (Harlow publishing, UK). Tonsillar size was assessed using the Brodsky classification.

*Home pulse oximetry:* The Masimo Radical 7 device (Masimo Corporation, Irvine, CA) was demonstrated. Written illustrated instructions were provided, with sensor placement on the great toe. The device recorded with a 1Hz sampling rate and a 2-second averaging time.

*Home cardiorespiratory polygraphy*: OSA was assessed on a separate night using the SOMNOtouch device (Somnomedics, Germany) as previously described23 comprising: chest and abdominal respiratory inductance plethysmography; pulse oximetry; nasal pressure flow with snore sensor; body position sensor; and actigraphy. A sleep log recorded sleep onset, night wakings and morning wake up times.

*Scoring of sleep studies*

Oximetry: Data were analysed blinded to the child’s clinical status using Visidownload software (Stowood Scientific, Oxford, UK). Artefact (low signal, poor perfusion, sensor displacement) and wake periods (sleep log) were extracted. Studies with < 4h of artefact-free (AF) data were rejected. Standard parameters were generated including: total AF time analysed; mean SpO2, minimum SpO2, 3% ODI, delta 12 second index (the absolute difference between successive 12-sec interval recordings, a measure of baseline SpO2 variability) and time in minutes/AF hour with SpO2 below 90%.

Cardiorespiratory polygraphy: Studies were scored by a technologist (RK), blinded to the clinical status of the child, using Domino Light software (Somnomedics, Germany) according to published criteria[[28]](#endnote-24). Every 10th study was independently re-scored, achieving an inter-rater reliability coefficient of 0.917 (95% CI 0.791 to 0.969) for the OAHI. Studies with < 4h of AF data[[29]](#endnote-25) were rejected.. The obstructive apnoea/hypopnoea index (OAHI) was calculated by summing obstructive apnoea, hypopnoea, mixed and undefined apnoea indices during the total sleep time. OSA was diagnosed if OAHI was > 5/h, a meaningful threshold for clinical intervention[[30]](#endnote-26) reflecting the sensitivity of domiciliary cardiorespiratory polygraphy in children[[31]](#endnote-27).

**Clinical validation data-set**

Data from 57 children with DS, clinically evaluated for OSA in Southampton between December 2014 and March 2017, were studied retrospectively. All children had Masimo pulse oximetry and cardiorespiratory polygraphy. Sensors, analysis software, scoring and quality criteria were identical to the training data-set. Seven children who were in the training data-set were excluded. The remaining 50 (26 male) were aged 2 months to 17.5 years (median 64.5 months). Data were anonymised and shared in accordance with UK Department of Health guidance for research ethics[[32]](#endnote-28).

**Sample size**

Training data-set sample size was estimated at 180 participants to achieve 150 complete studies based on clinical experience[[33]](#endnote-29) and data in adults20.

**Statistical analysis**

Statistical analysis was conducted in SPSS v 24 (IBM), with dotplots and confidence intervals (CIs) around proportions and likelihood ratios, obtained from Stata. Clinical characteristics, OAHI and SpO2 parameter distributions were described with descriptive statistics. Receiver Operating Characteristic (ROC) curves were drawn for SpO2 parameters as a predictor of OSA status in the training data set. Area Under the Curve (AUC) statistics were calculated with 95% CIs: an AUC=0.5 indicates no predictive power, an AUC=1.0, perfect prediction. SpO2 parameter threshold choice prioritised sensitivity over specificity to identify as many true positives as possible. Sensitivity, specificity, positive (+ve) and negative (-ve) likelihood ratios, at these thresholds, are presented with 95% CIs. All combinations of the SpO2 parameters were examined in logistic regression models with OSA status as the dependent variable. Resultant combined scores were standardised to have zero mean and unit standard deviation across the OSA groups combined. ROC curves, AUC statistics, and diagnostic performance of the standardised scores were evaluated as above. The sensitivity and specificity of the univariate and combined SpO2 parameter thresholds were assessed in the clinical validation data set.

### RESULTS

**Training data set**

*Participant characteristics*

In total 171/202 (85%) participants had both a successful cardiorespiratory and HPO study. Expert consensus was that 28d was a reasonable maximum interval between measures, as OAHI would be stable over this time-frame. This excluded 10/171 participants. For the majority of children in the final training sample (148/161, 92%) the maximum time interval between measures was 6 days and the longest interval across the entire sample was 23 days (n=1). Tables 1 and 2 illustrate demographic, cardiorespiratory polygraphy and SpO2 data for children with and without OSA.

**Table 1: Demographic and cardio-respiratory variables in children with and without OSA in the training data set. Figures are number (%) unless stated otherwise.**

|  |  |  |  |
| --- | --- | --- | --- |
|  |  | **No OSA**  **(n=136)** | **OSA**  **(n=25)** |
| **Age (months)** | **mean(SD)**  **min to max** | 36.3 (20.8)  6 to 71 | 33.9 (22.3)  6 to 71 |
| **Gender (M: F)** | **male**  **female** | 69 (51%)  67 (49%) | 17 (68%)  8 (32%) |
| **Snores regularly (always/almost always)** | | 39/135 (29%) | 13/24 (54%) |
| **Brodsky grading\*** | **grade 0-2**  **grade 3-4**  **tonsils removed**  **uncooperative or missing** | 55 (51%)  33 (31%)  20 (19%)  28 | 8 (50%)  5 (31%)  3 (19%)  9 |
| **BMI centile†** | **normal**  **underweight**  **overweight**  **obese**  **uncooperative or missing** | 4 (5%)  64 (75%)  6 (7%)  11 (13%)  4 | 0  12 (86%)  0  2 (12%)  0 |
| **Artefact-free (AF) data (hours)** | **median (mean)**  **min to max** | 8.6 (8.4)  4.5 to 11.2 | 8.7 (8.5)  5.3 to 10.6 |
| **Obstructive apnoea index** | **median (mean)**  **min to max** | 0.1 (0.4)  0 to 2.9 | 4.7 (8.0)  0 to 48.3 |
| **Obstructive hypopnoea index** | **median (mean)**  **min to max** | * 1. (0.4)   0 to 3.0 | 2.5 (4.0)  0 to 14.5 |
| **Central apnoea index** | **median (mean)**  **min to max** | 1.7 (2.2)  0 to 14.7 | 1.9 (3.1)  0.3 to 9.2 |
| **Mixed apnoea index** | **median (mean)**  **min to max** | 0 (0.1)  0 to 0.6 | 0.1 (0.3)  0 to 1.8 |
| **Undefined apnoea index** | **median (mean)**  **min to max** | 0.5 (0.8)  0 to 4.1 | 3.6 (9.1)  0 to 57.3 |
| **Obstructive apnoea/hypopnoea index** | **median (mean)**  **min to max** | 1.5 (1.6)  0.1 to 4.9 | 12.5 (21.4)  5.0 to 110.4 |
| **Number of nights between oximetry and polygraphy** | **1 night**  **2-6 nights**  **7-28 nights** | 96 (71%)  31 (23%)  9 (7%) | 17 (68%)  4 (16%)  4 (16%) |

**\* excluding uncooperative or missing from %s**

**† restricted to those aged ≥ 2 years and excluding uncooperative or missing from %s**

**Table 2: SpO2 parameters in children with and without OSA (training and validation data sets)**

|  |  |  |
| --- | --- | --- |
|  | **No OSA**  **Median, interquartile range and range** | **OSA**  **Median, interquartile range and range** |
| **Training data set** | **(n=136)** | **(n=25)** |
| **Artefact-free (AF) SpO2 data (hours)** | 10.0  8.4 to 11.0  5.0 to 13.0 | 9.5  8.4 to 10.1  5.3 to 11.6 |
| **Delta12 second index** | 0.51  0.43 to 0.59  0.20 to 1.31 | 0.69  0.61 to 0.88  0.39 to 3.70 |
| **3% ODI** | 5.32  3.51 to 7.65  0.10 to 40.10 | 11.44  8.47 to 18.20  2.06 to 106.92 |
| **SpO2 <90%**  **Minutes/AF hour** | 0.02  0.00 to 0.07  0.00 to 29.39 | 0.14  0.01 to 0.52  0.00 to 36.23 |
| **Mean SpO2** | 97.30  96.10 to 97.90  89.45 to 99.90 | 96.90  95.46 to 97.70  87.97 to 99.14 |
| **Minimum SpO2** | 87  83 to 90  61 to 95 | 85  81 to 88  47 to 93 |
| **Validation data set** | **(n=38)** | **(n=12)** |
| **Artefact-free (AF) SpO2 data (hours)** | 7.2  6.4 to 8.0  4.3 to 10.8 | 6.8  6.2 to 7.2  5.8 to 9.8 |
| **Delta12 second index** | 0.51  0.38 to 0.65  0.30 to 0.91 | 0.82  0.65 to 1.19  0.54 to 1.89 |
| **3% ODI** | 7.29  4.44 to 1.06  0.50 to 22.00 | 20.38  11.97 to 49.93  6.90 to 65.70 |
| **SpO2 <90%**  **Minutes/AF hour** | 0.15  0.00 to 0.13  0.00 to 38.33 | 1.71  0.04 to 1.71  0.01 to 40.81 |
| **Mean SpO2** | 96.7  95.73 to 97.92  91.72 to 98.46 | 94.9  92.35 to 97.56  86.17 to 98.63 |
| **Minimum SpO2** | 87.0  83.8 to 90  77 to 96 | 81.5  79 to 88  61 to 88 |

*Predictive value of oximetry indices (training data-set)*

Figure 1 presents the ROC curve and AUC statistic for SpO2 parameters as a predictor of OSA status. The greatest AUC was achieved by the delta 12 second index. At a threshold of >0.555 this identified 23/25 (sensitivity 92%) OSA cases and 89/136 true negatives (specificity 65%). The same sensitivity was achieved for 3% ODI with marginally lower specificity of 63% (86/136 true negatives). OSA was missed in two children (an 11-month female and a 12-month male - OAHI 6.5 and 6.9/h respectively), both were ‘occasional’ snorers. The predictive power of other univariate SpO2 parameters was low (Figure 1c,1d,1e and Table 3). The optimal combined SpO2 parameter included the delta 12 second index, 3% ODI, mean and minimum SpO2 with a sensitivity of 96% and specificity of 59% (Figure 1f). The distribution of participants’ OAHI values for the delta 12 second index and combined score is illustrated in Figure 2.

**Clinical validation data set**

OSA was present in 12/50 children (9 male). Oximetry and cardiorespiratory studies were separated by no more than 1 day. Predicting OSA status based on the univariate and combined parameter thresholds identified by the training data set yielded the same sensitivity (92%) for the delta 12s index, with similar specificity (63% v 65%). One 8 year- old screened false negative with an OAHI of 7.6/hour. While the 3% ODI and combined score achieved 100% sensitivity, it was at the cost of lower specificity (63%v 39% and 53% v 59% respectively).

**Table3: Chosen threshold, sensitivity, specificity +ve and –ve likelihood ratios for each SpO2 parameter and best combination of parameters.**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | **Threshold indicative of OSA** | **Sensitivity** | **Specificity** | **+ve**  **Likelihood ratio** | **-ve**  **Likelihood ratio** |
| **Training data set (n=161)** | | | | | |
| **Delta12 s index** | ≥0.555 | 23/25  92% (74%, 99%) | 89/136  65% (57%, 73%) | 2.66  (2.06, 3.45) | 0.12  (0.03, 0.46) |
| **3% ODI** | ≥6.150 | 23/25  92% (74%, 99%) | 86/136  63% (55%, 71%) | 2.50  (1.95, 3.21) | 0.13  (0.03, 0.48) |
| **SpO2 <90% minutes/AF hour** | ≥0.0645 | 15/25  60% (39%, 79%) | 98/136  72% (64%, 79%) | 2.15  (1.41, 3.22) | 0.55  (0.34, 0.91) |
| **Mean SpO2** | ≤97.175 | 18/25  72% (51%, 88%) | 75/136  55% (46%, 64%) | 1.61  (1.18, 2.18) | 0.51  (0.27, 0.97) |
| **Minimum SpO2** | ≤88.50 | 21/25  84% (64%, 95%) | 50/136  37% (29%, 45%) | 1.33  (1.07, 1.64) | 0.44  (0.17, 1.10) |
| **Combined score**  **See \* for computation** | ≥ -0.5537 | 24/25  96% (80%, 100%) | 80/136  59% (50%, 67%) | 2.33  (1.88, 2.89) | 0.07  (0.01, 0.47) |  |
| **Validation data set (n=50)** | | | |  | |
| **Delta12 s index** | ≥0.555 | 11/12  92% (62%, 100%) | 24/38  63% (46%, 78%) |
| **3% ODI** | ≥6.150 | 12/12  100% (74%, 100%) | 15/38  39% (24%, 57%) |
| **SpO2 <90% minutes/AF hour** | ≥0.0645 | 8/12  67% (35%, 90%) | 27/38  71% (54%, 85%) |
| **Mean SpO2** | ≤97.175 | 9/12  75% (43%, 95%) | 15/38  39% (24%, 57%) |
| **Minimum SpO2** | ≤88.50 | 12/12  100% (74%, 100%) | 17/38  45% (39%, 62%) |
| **Combined score**  **See \* for computation** | ≥ -0.5537 | 12/12  100% (74%, 100%) | 20/38  53% (36%, 69%) |  | |

\***Combined score formula**: - 20.988 + 1.408 x delta 12s index + 0.066x 3% ODI + 0.178 x mean SpO2 + 0.023 x minimum SpO2

### DISCUSSION

We have identified oximetry parameters that discriminate children with DS at risk of moderate to severe OSA. The best single parameter, delta 12s index > 0.555, a measure of baseline SpO2 variability, predicted OSA with high sensitivity (92%), and adequate specificity (65%, 63%) in training and validation data-sets respectively. 3% ODI lost specificity in the validation data-set so may be a less useful parameter. The combined model (delta 12s index, 3% ODI, mean and minimum SpO2) performed well in the validation data-set, detecting all true positives (100% sensitivity) but with lower specificity (53%). This would signpost 60% (12 true positives and 18 false negatives) to confirmatory multi-channel studies. Use of the consistently best predictor, the delta 12 second index, as a screening tool would halve the number of children needing confirmatory diagnostic multi-channel sleep studies.

McGill scoring criteria, based on identification of clusters of desaturation events, have been applied to oximetry traces extracted from in-lab polysomnography in 119 children with DS referred for evaluation of OSA17. McGill scores of 3 and 4 in 17 children had 98% specificity for mild OSA (OAHI > 2.5/h). Sensitivity data were not reported but appeared low (36.1% of children had McGill scores of 2, median OAHI 4.5/h). This suggests that McGill criteria have limited utility in a universal screening programme.

**Limitations**

Our findings specifically apply to parameters generated by Masimo oximeters and cannot be generalised to other devices. Masimo technology extracts motion artefact[[34]](#endnote-30), this is important in children with DS who are restless sleepers[[35]](#endnote-31).

Use of cardiorespiratory polygraphy rather than polysomnography to define OSA will have under-estimated hypopnoea associated with arousal, but not with oxyhemoglobin desaturation. The choice of cardiorespiratory polygraphy was pragmatic, reflecting a trade-off between optimal technology use and compliance in young children with developmental disorders as well as the reality of limited polysomnography provision in much of the world17,[[36]](#endnote-32).

Finally, the use of a retrospective clinical data-set, with anonymous data shared for this analysis, limits our information on the wider sampling frame, demographic and clinical characteristics of these children.

**Summary and recommendations for future research**

Despite almost a decade of recommendations, there are no agreed screening guidelines for OSA in DS in the UK. A simple oximetry parameter, the delta 12s index, yields 92% sensitivity to identify children at risk of moderate to severe OSA. It is important to note that oximetry alone cannot be used as a diagnostic tool and all children who screen positive need confirmatory multi-channel sleep studies. The delta 12s index offers the advantage over the McGill scoring criteria, of simplicity and does not rely on expert interpretation17. These findings need to be replicated in a larger sample and a new setting alongside measures of acceptability and costs[[37]](#endnote-33). Cost estimations should consider the need to repeat failed studies. Universal screening for OSA in children with Down syndrome using simple pulse oximetry parameters could halve the number of children requiring specialist multi-channel studies. Pulse oximetry is widely available, well tolerated, readily acquired in the home and its adoption could reduce the burden on health services and families alike.

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**Competing Interest:** Dr Hill received a no obligation loan of Masimo pulse oximeters used in the study. These devices were part of the original study design prior to the loan agreement. No competing interests are declared by co-authors

**Contributorship statement**: CMH, HE, MF, PG, RK, and HE developed the protocol. JM, JR and AJ supported recruitment, data collection and data entry. RK developed quality standards for sleep study acquisition and analysis. RK and JG analysed the cardiorespiratory studies. RP conducted the data analysis and produced tables and figures. HE provided the clinical validation data-set. CMH authored the manuscript which was reviewed by all authors.

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