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Home oximetry to screen for obstructive sleep apnoea in Down syndrome

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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 multichannel sleep studies. We aimed to determine whether home pulse oximetry (HPO) discriminates children at high risk of OSA, who need further diagnostic multichannel 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 multichannel 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 12 s 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 12 s index, 3% ODI, mean and 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 12 s index, a measure of baseline SpO2 variability (sensitivity 92%; specificity 63%).

Conclusions HPO screening could halve the number of children with Down syndrome needing multichannel 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.

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,4–5 can impair school performance,4,5,14 can have physical health consequences,4,5,14–18 and disproportionately affect cognitive and academic performance.2,19 Apnoea in DS can present at any age, and early diagnosis is recommended for the management of complications.19,20

Children with DS are at increased risk of severe OSA,19,21,22 which is associated with poor sleep architecture, sleep fragmentation, and increased apnoea index compared with non-DS controls.19,23,24 Obstructive sleep apnoea is associated with decreased quality of life,25–27 increased healthcare use,19,28–30 and long-term cardiorespiratory consequences,28,31–33 including increased cardiovascular disease risk.33,34 OSA can be detected during the neonatal period,35,36 and objective diagnosis is recommended5 annual screening with pulse oximetry to age 6 years followed by confirmatory multichannel sleep studies (polysomnography18 or cardiorespiratory polygraphy36) for abnormal oximetry studies. Multichannel 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 adults28 but not yet in children. A decade after the UK recommendations were made, there are no screening guidelines for OSA in children with DS.21,22

What is already known on this topic?

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

What this study adds?

- Simple numeric oximetry parameters can sensitively detect most children at risk of clinically significant obstructive sleep apnoea.
- Universal oximetry screening is widely available and could halve the number of children needing confirmatory multichannel sleep studies at specialist centres.
- The use of a simple screening threshold (the delta 12 s index) offers a screening approach that is accessible to the non-specialist paediatrician.
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We aimed to:
1. Identify home pulse oximetry (HPO) parameters that sensitively detect children at risk of OSA, therefore needing diagnostic multichannel studies, using research participants (training dataset);
2. Test how well these HPO parameters performed in a clinical setting (validation dataset);
3. Generate practical recommendations for OSA screening in children with DS.

METHODS

Training dataset

Inclusion and exclusion criteria
Eligible children had DS and were aged 6 months to 6 years. A history of ear, nose and throat 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
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. 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 aged >2 years (Harlow Publishing, UK). Tonsillar size was assessed using the Brodsky classification.

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

Home cardiorespiratory polygraphy
OSA was assessed on a separate night using the SOMNOtouch device (Somnomedics, Germany) as previously described 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 <4 hours of artefact-free (AF) data were rejected. Standard parameters were generated including: total AF time analysed; mean SpO2, minimum SpO2, 3% oxyhaemoglobin desaturation index (ODI), delta 12 s index (the absolute difference between successive 12 s interval recordings, a measure of baseline SpO2 variability) and time in min/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) according to published criteria. Every 10th study was independently rescored, achieving an inter-rater reliability coefficient of 0.917 (95% CI 0.791 to 0.969) for the obstructive apnoea/hypopnoea index (OAHI). Studies with <4 hours of AF data were rejected. The 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/hour, a meaningful threshold for clinical intervention reflecting the sensitivity of domiciliary cardiorespiratory polygraphy in children.

Clinical validation dataset

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 dataset. Seven children who were in the training dataset were excluded. The remaining 50 (26 males) were aged 2 months to 17.5 years (median 64.5 months). Data were anonymised and shared in accordance with the UK Department of Health guidance for research ethics.

Sample size

Training dataset sample size was estimated at 180 participants to achieve 150 complete studies based on clinical experience and data in adults.

Statistical analysis

Statistical analysis was conducted in SPSS V24 (IBM), with dot plots and CI 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 dataset. Area under the curve (AUC) statistics were calculated with 95% CIs: an AUC=0.5 indicates no predictive power, an AUC=1.0 indicates 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 SD 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 dataset.

**RESULTS**

**Training dataset**

**Participant characteristics**

In total, 171/202 (85%) participants had both a successful cardiorespiratory and HPO study. Expert consensus was that 28 days 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.

**Predictive value of oximetry indices (training dataset)**

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 12s 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/hour, respectively), both were ‘occasional’ snorers. The predictive power of other univariate SpO₂ parameters was low (figure specific, specificity of 59% (figure score is illustrated in figure pants’ OAHI values for the delta 12

**Clinical validation dataset**

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 dataset yielded the same sensitivity (92%) for the delta 12s index, with similar specificity (63% vs 65%). One child aged 8 years 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% vs 39% and 53% vs 59%, respectively).

**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 datasets, respectively. Three per cent ODI and combined score achieved 100% specificity, it was at the cost of lower specificity (63% vs 39% and 53% vs 59%, respectively).

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 OSA. McGill scores of 3 and 4 in 17 children had 98% specificity for mild OSA (OAHI >2.5/
hour). Sensitivity data were not reported but appeared low (36.1% of children had McGill scores of 2, median OAHI 4.5/hour). 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, this is important in children with DS who are restless sleepers. Use of cardiorespiratory polygraphy rather than polysomnography to define OSA will have underestimated hypopnoea associated with arousal, but not with oxyhaemoglobin 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 world.

Finally, the use of a retrospective clinical dataset, 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 multichannel sleep studies. The delta 12s index offers the advantage over the McGill scoring criteria, of simplicity and does not rely on expert interpretation. These findings need to be replicated in a larger sample and a new setting alongside measures of acceptability and costs. Cost estimations should consider the need to repeat failed studies. Universal screening for OSA in children with DS using simple pulse oximetry parameters could halve the number of children requiring specialist multichannel studies. Pulse oximetry is...
Table 3  Chosen threshold, sensitivity, specificity, +ve and −ve likelihood ratios for each SpO2 parameter and best combination of parameters

<table>
<thead>
<tr>
<th>Threshold indicative of OSA</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>+ve Likelihood ratio</th>
<th>−ve Likelihood ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delta 12 s index ≥0.555</td>
<td>23/25</td>
<td>89/136</td>
<td>2.66</td>
<td>0.12</td>
</tr>
<tr>
<td>92% (74%, 99%)</td>
<td>65% (57%, 73%)</td>
<td></td>
<td>(2.06, 3.45)</td>
<td>(0.03, 0.46)</td>
</tr>
<tr>
<td>3% ODI ≥6.150</td>
<td>23/25</td>
<td>86/136</td>
<td>2.50</td>
<td>0.13</td>
</tr>
<tr>
<td>92% (74%, 99%)</td>
<td>63% (55%, 71%)</td>
<td></td>
<td>(1.95, 3.21)</td>
<td>(0.03, 0.48)</td>
</tr>
<tr>
<td>SpO2&lt;90% min/AF hour ≥0.0645</td>
<td>15/25</td>
<td>98/136</td>
<td>2.15</td>
<td>0.55</td>
</tr>
<tr>
<td>60% (39%, 79%)</td>
<td>72% (64%, 79%)</td>
<td></td>
<td>(1.41, 3.22)</td>
<td>(0.34, 0.91)</td>
</tr>
<tr>
<td>Mean SpO2 ≤97.175</td>
<td>18/25</td>
<td>75/136</td>
<td>1.61</td>
<td>0.51</td>
</tr>
<tr>
<td>72% (51%, 88%)</td>
<td>55% (46%, 64%)</td>
<td></td>
<td>(1.18, 2.18)</td>
<td>(0.27, 0.97)</td>
</tr>
<tr>
<td>Minimum SpO2 ≤88.50</td>
<td>21/25</td>
<td>50/136</td>
<td>1.33</td>
<td>0.44</td>
</tr>
<tr>
<td>84% (64%, 95%)</td>
<td>37% (29%, 45%)</td>
<td></td>
<td>(1.07, 1.64)</td>
<td>(0.17, 1.10)</td>
</tr>
<tr>
<td>Combined score ≥−0.5537</td>
<td>24/25</td>
<td>80/136</td>
<td>2.33</td>
<td>0.07</td>
</tr>
<tr>
<td>See * for computation</td>
<td>96% (80%, 100%)</td>
<td></td>
<td>(1.88, 2.89)</td>
<td>(0.01, 0.47)</td>
</tr>
</tbody>
</table>

Validation dataset (n=50)

<table>
<thead>
<tr>
<th>Threshold indicative of OSA</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>+ve Likelihood ratio</th>
<th>−ve Likelihood ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delta 12 s index ≥0.555</td>
<td>11/12</td>
<td>24/38</td>
<td>63% (46%, 78%)</td>
<td></td>
</tr>
<tr>
<td>92% (62%, 100%)</td>
<td></td>
<td></td>
<td>(24%, 57%)</td>
<td></td>
</tr>
<tr>
<td>3% ODI ≥6.150</td>
<td>12/12</td>
<td>15/38</td>
<td>63% (46%, 78%)</td>
<td></td>
</tr>
<tr>
<td>100% (74%, 100%)</td>
<td></td>
<td></td>
<td>(24%, 57%)</td>
<td></td>
</tr>
<tr>
<td>SpO2&lt;90% min/AF hour ≥0.0645</td>
<td>8/12</td>
<td>27/38</td>
<td>71% (54%, 85%)</td>
<td></td>
</tr>
<tr>
<td>67% (35%, 90%)</td>
<td></td>
<td></td>
<td>(24%, 57%)</td>
<td></td>
</tr>
<tr>
<td>Mean SpO2 ≤97.175</td>
<td>9/12</td>
<td>15/38</td>
<td>39% (24%, 57%)</td>
<td></td>
</tr>
<tr>
<td>75% (43%, 95%)</td>
<td></td>
<td></td>
<td>(24%, 57%)</td>
<td></td>
</tr>
<tr>
<td>Minimum SpO2 ≤88.50</td>
<td>12/12</td>
<td>17/38</td>
<td>45% (39%, 62%)</td>
<td></td>
</tr>
<tr>
<td>100% (74%, 100%)</td>
<td></td>
<td></td>
<td>(36%, 69%)</td>
<td></td>
</tr>
<tr>
<td>Combined score</td>
<td>12/12</td>
<td>20/38</td>
<td>53% (36%, 69%)</td>
<td></td>
</tr>
<tr>
<td>See * for computation</td>
<td>100% (74%, 100%)</td>
<td></td>
<td>(0.01, 0.47)</td>
<td></td>
</tr>
</tbody>
</table>

*Combined score formula: −20.988+1.408×delta 12 s index+0.066×3% ODI+0.178×mean SpO2+0.023×minimum SpO2.

AF, artefact-free; ODI, oxyhaemoglobin desaturation index; OSA, obstructive sleep apnoea.

Figure 2  Dot plots of delta 12 s and the combined score shown for training set (n=161) of children with and without obstructive sleep apnoea (OSA). AF, artefact-free; ODI, oxyhaemoglobin desaturation index.
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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Contributors CMH, HEE, HJE, RMP and PG designed the study protocol, applied for funding, agreed standard operating procedures, supervised data collection and clinical interpretation of findings in their respective centres and contributed intellectually to the authorship of the paper. RMP performed the data analysis for the training data set and checked the analysis for the clinical data set performed by CMH, who wrote the first draft of the manuscript. RNK developed the polygraphy set up and scoring protocol, undertook data analysis of all polygraphy studies in the training set. JGG performed inter-rater scoring of the training data set polygraphy and supervised and allowed access to the clinical data set JM, JR and AJ recruited training set participants, undertook Masimo study analysis and data entry. All authors reviewed and agreed the manuscript.

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Competing interests CMH received 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.

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

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement No data are available at present as we are continuing to analyse other aspects of the study data set.

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REFERENCES