Predictors of sleep disordered breathing in children with Down syndrome: a systematic review and meta-analysis

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Shareable abstract (@ERSpublications)
This review identified several predictors of sleep disordered breathing (SDB) in children with Down syndrome. Meta-analysis identified older age as a predictor. This supports routine longitudinal screening of all children with Down syndrome for SDB. https://bit.ly/3KGnqFK

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Abstract

Children with Down syndrome are at increased risk of sleep disordered breathing (SDB). SDB is associated with significant morbidity including neurocognitive impairment, cardiometabolic disease and systemic inflammation. The identification of clinical markers that may predict SDB is critical in facilitating early diagnosis and treatment, and ultimately, preventing morbidity. The objective of this systematic review was to identify predictors of SDB in patients with Down syndrome. A search was conducted using MEDLINE, Embase, the Cochrane Central Register of Controlled Trials and the Cumulative Index to Nursing and Allied Health Literature. A meta-analysis was performed according to the Meta-analyses of Observational Studies in Epidemiology checklist. Our review of the literature identified inconsistent associations between a variety of variables and SDB in children with Down syndrome, although the quality of evidence was poor. Meta-analysis of age and sex identified that children with OSA were older than those without OSA, and there was a similar risk of OSA in males and females, although risk favoured males. Currently, the American Academy of Pediatrics guidelines recommend that children with Down syndrome undergo polysomnography by the age of 4 years. Our review supports the recommendation for routine screening of children with Down syndrome. However, results from our meta-analysis suggest a need for longitudinal screening to diagnose children who may develop SDB as they get older.

Introduction

Sleep disordered breathing (SDB) is used to describe a group of disorders characterised by abnormal respiratory patterns or insufficient ventilation during sleep [1]. The most common type of SDB is obstructive sleep apnoea (OSA), which is caused by obstruction of the upper airway during sleep [2]. Central sleep apnoea (CSA) and nocturnal hypoventilation are less common in this population. SDB occurs more frequently in children with Down syndrome (prevalence 31–63%) as compared to the general paediatric population (prevalence 0.7–13.0%) [2–4]. Children with Down syndrome are at increased risk of SDB due to characteristics commonly associated with Down syndrome such as small oropharynx, narrow upper airway structure, mid-facial hypoplasia, relatively large tongue, obesity, hypothyroidism, generalised hypotonia and adenoidal and tonsillar hypertrophy [2, 5, 6].

SDB is associated with significant morbidity including neurocognitive impairment, cardiometabolic disease and systemic inflammation [7]. Children with Down syndrome are at further increased risk of morbidity secondary to cardiac complications such as pulmonary and systemic hypertension, as well as metabolic complications such as insulin resistance [8].

The gold-standard test to diagnose SDB is an overnight laboratory polysomnogram (PSG) [9]. The current American Academy of Pediatrics guidelines recommend that at least one PSG be performed in children

with Down syndrome before the age of 4 years [10, 11]. However, due to limited resources, this requirement is often difficult to fulfil. Paediatric PSGs are routinely performed at tertiary care children's hospitals, which have excessively lengthy wait lists [10]. Additionally, children with Down syndrome may have barriers to successfully completing PSG, including neurocognitive and psychiatric comorbidities that make it difficult to adapt to the sleep laboratory environment [12].

The identification of clinical symptoms and features that can help predict SDB is critical in facilitating early diagnosis and treatment, and ultimately, preventing life-threatening comorbidities. This will enable children at greatest risk to be prioritised for definitive testing with PSG, so that rapid identification and treatment can occur. The objective of this systematic review was therefore to identify and summarise existing data on predictors of SDB in children with Down syndrome.

Methods

Search strategy

This systematic review was designed using the Meta-analyses of Observational Studies in Epidemiology checklist and registered with the International Prospective Register of Systematic Reviews (registration number CRD42017070489). The search strategy was developed and conducted with the help of an information specialist. Keywords were derived from the terms "sleep disordered breathing", "Down syndrome" and "trisomy 21". A comprehensive literature search was conducted using MEDLINE, Embase, the Cochrane Central Register of Controlled Trials and the Cumulative Index to Nursing and Allied Health Literature from inception to 30 April 2021 (supplementary table A1).

Study selection

After de-duplication, retrieved records were uploaded to CrowdScreen and Covidence, online platforms to facilitate screening. Screening and data abstraction occurred independently and in duplicate by two reviewers at each phase of the review (Y. Hanna, J. Bokhaut, N. Hanna, H. Blinder), with discrepancies resolved by consensus, and if a consensus wasn't reached, then by a clinical expert (S. Katz). Selection consisted of two phases: title and abstract screening, followed by the full-text screening of articles. During the title and abstract screening phase of the review, studies identified as eligible by at least one reviewer were included for full-text screening.

We included studies that met the following criteria: 1) included individuals with Down syndrome who were evaluated for SDB using overnight laboratory-based PSG; 2) identified and reported quantitative data on clinical predictors of SDB in individuals with Down syndrome; and 3) were peer-reviewed, including randomised controlled trials, retrospective and prospective cohort studies, case series, cross-sectional studies and qualitative studies. We excluded studies that did not exclusively evaluate children with Down syndrome unless subgroup data for the population with Down syndrome was available. In addition, we excluded case reports (studies with a sample size less than five), protocols, guidelines, letters to the editor and studies not in the English language.

Data collection and risk of bias

Study selection and assessment of the risk of bias was undertaken by two sets of independent reviewers (Y. Hanna, J. Bokhaut, N. Hanna, H. Blinder). Disagreement was resolved through discussion between the reviewers to reach a consensus. If a consensus was not reached, the principal investigator was consulted.

Data collection process

All final data collection was performed using REDCap, a secure online electronic database [13]. Data extraction was performed independently by two reviewers. A standard abstraction form was used which collected information on publication characteristics (study title, first author, year of publication, study timeframe, country of origin of study, source of funding), study characteristics (study design, study objectives, sample size, median age and range, percentage males, severity and type of SDB, definition of SDB, comorbidities), predictors assessed and associated regression estimates.

Risk of bias

Risk of bias was assessed independently by two reviewers using the Quality in Prognosis Studies tool, which is the standard tool recommended by Cochrane to review cohort studies evaluating predictive factors for diagnosis or prognosis [14]. The overall risk of bias was evaluated according to the method reported by Lazzerini *et al.* [15]. An overall low risk of bias was given if all domains were scored as low, or if no more than two moderate/unknown risk of bias were identified. Moderate risk of bias was given when three or fewer risk of bias domains were scored moderate, in combination with no high risk of bias. A study was scored as moderate if one domain scored as high risk of bias in combination with one or fewer moderate

risk of bias. A high risk of bias was given when two or more domains scored a high risk, or four or more domains were scored as having a moderate risk of bias.

Data analysis

Predictors were associated with SDB if the p-values did not cross the null hypothesis, or when p-values were not available, predictors were considered to be associated based on the authors' reporting. Associations were positive if both variables moved in the same direction, and negative if the variables moved in the opposite direction. Appropriateness of pooling was assessed by examining studies for clinical and statistical heterogeneity. Clinical heterogeneity was based on baseline characteristics such as severity and type of SDB, definition of SDB used to identify predictors and age. Specifically, predictors were pooled only for studies evaluating the same type of SDB. Studies defining OSA using apnoea–hypopnoea index (AHI) or obstructive AHI (oAHI) cut-offs were pooled together. Statistical heterogeneity was defined by an I^2 statistic >75%. Where pooling of outcome data was appropriate, data were meta-analysed using a random-effects model. Results were presented as mean differences, odds ratios and/or relative risks with 95% confidence intervals for predictors. In the presence of clinical or statistical heterogeneity, pooling of data was not performed and the results were described qualitatively.

Results

The electronic search resulted in 770 independent records. After exclusions, we reviewed the full texts of 119 articles and 95 were excluded. 24 studies were included in the systematic review (supplementary figure A1).

Characteristics of included studies

The characteristics of each study are summarised in table 1. There were eight prospective studies, nine retrospective studies and seven cross-sectional studies. There were 22 studies which primarily investigated predictors of OSA, one which investigated predictors of CSA, and one which investigated nocturnal hypoventilation. Studies were published between 2003 and 2021 and included 2063 patients. The diagnostic cut-offs used to define clinically significant SDB were AHI >1–5 events·h^{-1} or oAHI >1–2 events·h^{-1}.

Risk of bias

A summary of the methodological quality of the studies is shown in figure 1. Overall, the methodological quality was high, with 19 studies having a low risk of bias (79%), four having a moderate risk of bias (17%) and the remaining study having a high risk of bias (4%). The most frequent sources of bias were selection bias (related to lack of description of study participation), attrition bias (related to lack of response rate recording or description of those lost to follow-up) and measurement bias of predictors (related to lack of valid and reliable measurement of predictors).

Variables evaluated as predictors for SDB

A summary of all predictors of SDB evaluated in the included studies can be found in supplementary table A2. A summary of all predictors for which at least one study reported a positive or negative association with SDB can be found in table 2.

Demographics

Age

Overall, nine studies evaluated the relationship between age and AHI [4, 8, 20–23, 27, 34, 35]. Five studies did not find a significant association between age and presence of OSA or AHI [8, 20–23]. There were two studies that reported a positive association between age and OSA [19, 27]. Shires *et al.* [34] found that patients with OSA had a higher mean age, while Lee *et al.* [27] identified a higher median age in children with OSA compared to those without OSA. Conversely, Skotko *et al.* [35] dichotomised children according to age: <8 years and ⩾8 years, and identified a significant association between younger age and presence of OSA. de Miguel-Díez [4] *et al.*, who used a cut-off of AHI >3 events·h^{-1} for OSA, also reported inverse associations between age and OSA. This study identified a lower mean age of patients with OSA, and an inverse relationship between AHI and age when evaluated continuously [4]. When dichotomising children to ages <8 years and ⩾8 years, younger age was positively associated with presence of OSA [4].

Four studies evaluated the relationship between age and oAHI [8, 29, 33, 36]. Rosen *et al.* [33] identified a positive association between median age and presence of OSA when comparing patients without OSA to those with mild or moderate OSA. Waters *et al.* [36] dichotomised children into <2 years or ⩾2 years and reported a negative relationship between age and presence and severity of OSA. There were two studies which reported conflicting associations between age and OSA [8, 29]. Nehme *et al.* [8] reported a positive

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TABLE 1 Description of studies

First author, year [ref.]	Design	Subjects n	SDB definition with respect to predictor	SDB	Indices of SDB severity	Age years	Objective
Anand, 2021 [16]	Prospective cross-sectional	53	OSA: AHI ⩾1 events·h^{-1}	96	Mean±SD AHI 8.96±1.8 events·h^{-1}	Mean (range) 5.9 (3–11.8)	1) Assess the effect of quality of sleep on development and behaviour of children with trisomy 21 2) Assess the effect of sleep apnoea on development and behaviour of children with trisomy 21
Austeng, 2014 [17]	Cross-sectional	29	OSA: OAI/AHI >1.5 events·h^{-1}	AHI >1.5 events·h^{-1} 97% OAI >1.5 events·h^{-1} 69%	Mean±SD AHI 10±8.8 events·h^{-1}	Mean 8	1) Measure prevalence and medical follow-up of OSA in young children with Down syndrome 2) Identify the association between OSA and age, BMI and airway surgery
Banjar, 2013 [18]	Prospective cohort	23	OSA: AHI >1 events·h^{-1}	82.6%	Mean AHI 12.3 events·h^{-1} Mean OAI 4.73 events·h^{-1}	Not reported	Identify sleep abnormalities in children with Down syndrome
Basil, 2016 [19]	Retrospective cohort	303	OSAS: AHI ⩾2 events·h^{-1}	74%	Mild OSAS: 38.9% Moderate OSAS: 32.8% Severe OSAS: 28.2%	Mean±SD (range) 10.6±4.06 (2–18)	1) Investigate whether children with Down syndrome are at increased risk of obesity 2) Explore OSAS, which is associated with obesity in children with Down syndrome
Breslin, 2014 [20]	Prospective cohort	38	OSAS: AHI >1.5 events·h^{-1}	61%	Mean±SD AHI 5.79±9.86 events·h^{-1}	Mean±SD (range) 9.6±.8 (7–12)	1) Investigate the association between OSAS and cognition in children with Down syndrome 2) Investigate the effect of OSAS on sleep physiology in children with Down syndrome
Brooks, 2015 [21]	Prospective cohort	25	OSA: AHI ⩾5 events·h^{-1}	40%	Mean±SD AHI 13.42±15.89 events·h^{-1}	Mean±SD (range) 10.14±3.39 (7.2–18.7)	1) Investigate the effect of sleep and SDB on neuropsychological functioning of children with Down syndrome 2) Determine whether treatment of SDB improves cognitive functioning
Chamseddin, 2019 [22]	Qualitative study with retrospective data collection	106	OSA: AHI ⩾1 events·h^{-1}	90%	Mean±SD AHI 16.7±6.25 events·h^{-1}	Mean±SD 7.3±4	1) To evaluate demographic, clinical and polysomnographic features of children with Down syndrome with clinical suspicion of OSA 2) Identify factors that predict OSA in children with Down syndrome
Durhan, 2019 [23]	Cross-sectional	18	OSA: AHI ⩾1 events·h^{-1}	61.1%	Mean AHI 3.23 events·h^{-1}	Median (IQR) 6.6 (4.4–10.5)	Determine the effect of OSA on periodontal and dental health in children with Down syndrome

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TABLE 1 Continued

First author, year [ref.]	Design	Subjects n	SDB definition with respect to predictor	SDB	Indices of SDB severity	Age years	Objective
Dyken, 2003 [9]	Prospective cohort	19	Sleep apnoea: apnoea index >1 event·h^{-1} and S_{aO_2} low point <92% (with baseline S_{aO_2} >92%)	79%	Median (IQR) AHI 6.0 (3–8) events·h^{-1} Median (IQR) apnoea index 3.0 (2–5) events·h^{-1}	Mean±SD 9.1±4.7	1) Investigate OSA in young Down syndrome patients using PSG 2) Identify the effects of therapy on OSA in young Down syndrome patients
Elsharkawi, 2017 [24]	Cross-sectional	101	OSA: AHI ⩾1 events·h^{-1}	42.6%	Mild OSA: 28% Moderate OSA: 2% Severe OSA: 13%	Mean±SD 9.1±4.0	1) Compare urinary biomarkers of children with Down syndrome to neurotypically healthy controls 2) Determine whether urinary biomarkers could predict a diagnosis of OSA
Friedman, 2018 [25]	Cross-sectional	113	OSA: AHI ⩾2 events·h^{-1}	Not reported	Mean AHI 13.76 events·h^{-1}	Mean 5.89	1) Assess parents' accuracy in reporting their children's breathing patterns 2) Assess risk factors associated with abnormal sleep study
Jayaratne, 2017 [26]	Qualitative study with prospective data collection	63	OSA: AHI >1 events·h^{-1}	44.2%	Not reported	Mean±SD (range) 7.49±4.86 (3.1–24.4)	1) Characterise the facial morphology of children with Down syndrome 2) Compare facial anthropometric characteristics of Down syndrome patients with published norms 3) Compare facial anthropometric characteristics of Down syndrome patients with and without OSA to predict OSA status in patients with Down syndrome
Lee, 2020 [27]	Cross-sectional	30	OSA: AHI ⩾1 events·h^{-1}	80%	Median (IQR) AHI 5.2 (1.7–15.7) events·h^{-1}	Median (IQR) 11.3 (9.4–15.6)	1) Measure the prevalence of OSA in children with Down syndrome 2) Identify the role of OSA and sleep structure in affecting cognitive performance
Maris, 2016 [28]	Cross-sectional	54	OSA: AHI⩾2 events·h^{-1}	57.1%	Median (IQR) AHI 7.25 (5.7–9.8) events·h^{-1}	Median (range) 7.5 (4–18)	1) Identify prevalence of sleep problems in children with Down syndrome as measured by Children's Sleep Habits Questionnaires 2) Compare prevalence of sleep problems in children with Down syndrome and controls 3) Investigate association between sleep problems and OSA

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TABLE 1 Continued

First author, year [ref.]	Design	Subjects n	SDB definition with respect to predictor	SDB	Indices of SDB severity	Age years	Objective
Maris, 2016 [29]	Cross-sectional	122	OSA: AHI ≥2 events·h^{-1}	66.4%	Median (IQR) AHI 8.2 (4.3–16.7) events·h^{-1}	Median (IQR) 5.0 (2.8–10.5)	1) Measure prevalence of OSA in children with Down syndrome 2) Identify factors that are associated with disease severity
de Miguel-Díez, 2003 [4]	Prospective cohort	108	OSA: AHI ≥3 events·h^{-1}	54.6%	Mean±SD AHI 6.1±6.7 events·h^{-1}	Mean±SD (range) 7.9±4.5 (1–18)	1) Measure the prevalence of SDB in children with Down syndrome 2) Identify factors that predispose children with Down syndrome to SDB
Naime, 2021 [30]	Retrospective cohort	158	CSA: CAI >2 events·h^{-1} OSAS: AHI >2 events·h^{-1}	79.1% OSAS 12% CSA	Median (IQR) CAI 0.20 (0.0–0.83) events·h^{-1} Median (IQR) AHI 5.95 (2.40–16.52) events·h^{-1}	Median (IQR) 4.8 (0.04–18.3) Median (IQR) 4.8 (2.31–9.02)	1) Identify clinical predictors of central breathing problems in children with Down syndrome 2) The role of sex and OSA status on presence of central breathing problems
Nehme, 2017 [8]	Retrospective cohort	119	OSA: AHI >5 events·h^{-1} Hypoventilation: carbon dioxide 50 mmHg for ⩾25% of total sleep time	42.9%	Median (IQR) AHI 3.6 (1.6–11.2) events·h^{-1}	Median (IQR) (range) 6.6 (4.4–10.5) (0.05–16.8)	Determine clinical predictors of SDB in children with Down syndrome
Posada, 2019 [31]	Qualitative study with retrospective data collection	53	OSA: AHI >2 events·h^{-1}	50.9%	Median (IQR) AHI: 0–23 months 7.0 (1.5–20.2) events·h^{-1} 24–84 months 8.3 (1.9–30.0) events·h^{-1} 85–156 months 8.4 (2.5–19.0) events·h^{-1} >156 months 13.0 (4.9–29.2) events·h^{-1}	Median (IQR) 3.4 (1.6–8.8)	Measure the incidence of sleep-related breathing disorders in children with Down syndrome living at high altitude
Richard, 2020 [32]	Retrospective case–control study	56	Nocturnal hypoventilation: >25% of total sleep time spent with a P_{tcCO_2} >50 mmHg	OSA 85.7% Nocturnal hypoventilation 17.9%	Median (IQR) AHI 5 (3–10.2) events·h^{-1} Median (IQR) mean P_{tcCO_2} 44 (43–46.5) mmHg	Median (IQR) 4.9 (2.0–7.8)	Compare P_{tcCO_2} and pulse oximetry (S_{pO_2}) in children with Down syndrome and in control children with clinical signs of OSA
Rosen, 2020 [33]	Qualitative study with retrospective data collection	418	OSA: AHI >1 events·h^{-1}	42.1%	Mean AHI 3.6 events·h^{-1} Median AHI 0.6 events·h^{-1}	Mean (range) 7.27 (2–17) Median 6	1) Identify the prevalence of increased periodic limb movements of sleep in children with Down syndrome 2) Determine the correlation of periodic limb movements of sleep with OSA and levels of ferritin
Shires, 2010 [34]	Retrospective cohort	52	OSA: AHI >1.0 events·h^{-1}	63.5%	Mean AHI 18.7 events·h^{-1}	Mean±SD 9.3±4.5	Identify the effect of body mass on the incidence of OSA in children with Down syndrome

Continued

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TABLE 1 Continued

First author, year [ref.]	Design	Subjects n	SDB definition with respect to predictor	SDB	Indices of SDB severity	Age years	Objective
Skotko, 2017 [35]	Prospective cohort	102	OSA: AHI >1 events·h^{-1}	44.1%	Not reported	Median (range) 5.6 (3–24.4)	To create a predictive model to help screen for OSA in children with Down syndrome
Waters, 2020 [36]	Qualitative study with retrospective data collection	152	OSA: AHI >2 events·h^{-1}	85.5%	Mean±SD AHI 13.1±22.4 events·h^{-1}	First PSG: mean±SD 5.0±4.3 Last PSG: mean±SD 8.2±5.1	Identify the spectrum of OSA in children with Down syndrome

SDB: sleep disordered breathing; OSA: obstructive sleep apnoea; AHI: apnoea–hypopnoea index; OAI: obstructive apnoea index; BMI: body mass index; OSAS: OSA syndrome; IQR: interquartile range; S_{aO_2}: arterial oxygen saturation; PSG: polysomnography; CSA: central sleep apnoea; CAI: central apnoea index; P_{tcCO_2}: transcutaneous partial pressure of carbon dioxide; S_{pO_2}: oxygen saturation measured by pulse oximetry.

relationship between age and the presence of oAHI >5 events·h^{-1} but this association was not maintained when age was dichotomised to ⩾4 years or <4 years [8]. Maris *et al.* [29] reported a weak inverse correlation between age and oAHI when evaluated continuously, but when the oAHI was evaluated among three different age groups (0–4.9 years, 5–11.9 years and 12–28 years), no differences in prevalence of OSA or median oAHI were identified.

There were two studies that evaluated the relationship between age and the central apnoea index (CAI) [22, 30]. Chamseddin *et al.* [22] did not find a difference between older and younger children when comparing mean CAI. Naime *et al.* [30] reported that a higher percentage of children aged <2 years had a diagnosis of CSA, when compared to children in the 3–10 years and >10 years age groups.

Richard *et al.* [32] evaluated the relationship between age and nocturnal hypoventilation, but found no difference in the median age between participants with and without nocturnal hypoventilation.

Meta-analysis of the association between age and OSA

A total of three studies with a cumulative total of 108 participants were included in our meta-analysis (figure 2) [20, 23, 34]. The pooled data identified that children with OSA were 1.52 years (95% CI 0.57–2.46 years) older than children without OSA. Participants included in the studies pooled in this meta-analysis were mostly aged >4 years.

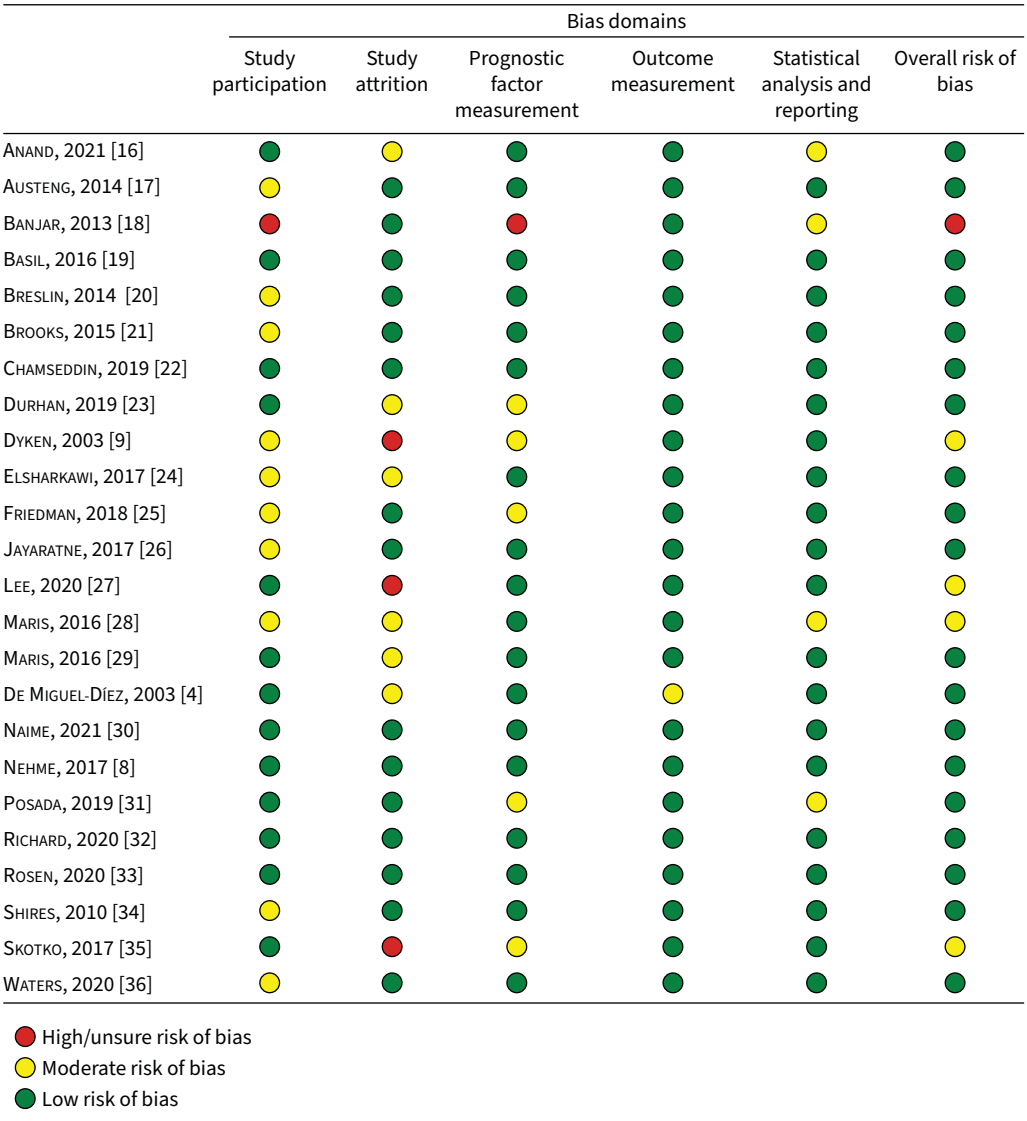

FIGURE 1 Risk-of-bias assessment (Quality in Prognosis Studies) tool.

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TABLE 2 Summary of associations by study for selected predictors of sleep disordered breathing (SDB)

	AHI			oAHI			CAI			Nocturnal hypoventilation		
	Positive association	Negative association	No association	Positive association	Negative association	No association	Positive association	Negative association	No association	Positive association	Negative association	No association
Age	Shires [34], Lee [27]	de Miguel-Díez [4] (r= −0.195; OR=2.9), Skotko [35]#	Nehme [8], Breslin [20], Brooks [21], Durhan [23], Chamseddin [22], Skotko [35]# (d= −0.74)	Rosen [33], Nehme [8] (OR=1.14)	Maris [29] (r= −0.199), Waters [36] (Chi-squared=12.87)	Nehme [8], Maris [29]		Naime [30]	Chamseddin [22]			Richard [32]
Male sex	de Miguel-Díez [4] (OR=3.32)	Brooks [21]	Skotko [35], Shires [34], Austeng [17], Breslin [20] (OR=0.22), Lee [27]			Maris [29], Rosen [33]		Naime [30]#	Naime [30]#			
Body mass index	Shires [34]#, Dyken [9] (r=0.62), Basil [19] (risk ratios 2.4 and 1.4), Elsharkawi [24]#		Brooks [21], Lee [27], Skotko [35], Breslin [20] (d= −0.15; OR=0.73), Austeng [17], Shires [34]# (R^2=0.2), Elsharkawi [24]# (r=0.21), Durhan [23], de Miguel-Díez [4] (OR=0.7), Nehme [8]	Basil [19] (Spearman ρ=0.16)		Maris [29], Chamseddin [22], Nehme [8] (OR=0.71)						Richard [32]
Presence of GORD			Nehme [8] (OR=0.70), Shires [34]		Nehme [8] (OR=0.16)							
History of rhinitis/ rhinorrhoea/sinusitis			Nehme [8] (OR=2.13), Nehme [8] ($_{adjusted}$OR=2.38)	Nehme [8] ($_{adjusted}$4.49)		Nehme [8] (OR=2.22)						
Adenotonsillar hypertrophy	Shires [34] (r^2=0.75), de Miguel-Díez [4]# (OR=4.7)		Nehme [8] (OR=1.16), de Miguel-Díez [4]# (OR=0.4)			Maris [29], Nehme [8] (OR=1.26)						
Dental examinations	Durhan [23]#		Skotko [35], de Miguel-Díez [4], Durhan [23]#									
Parental questionnaires of sleep behaviours			Breslin [20] (d=0.56, d=0.51), Brooks [21], Nehme [8] (OR=0.79–2.38), Friedman [25]			Maris [28], Nehme [8] (OR=0.63–1.75), Brooks [21]						
Snoring			Banjar [18]	Posada [31]								
Parental questionnaires of neuropsychological or developmental function	Anand [16] (ρ=0.42–0.83	Breslin [20] (d=0.91)	Lee [27], Brooks [21], Breslin [20] (t: Mann–Whitney U=0.42–1.03, d=0.16–0.36)									
Cognitive function	Anand [16]#, Breslin [20]# (t: Mann–Whitney U=55.50, d=1.06)	Anand [16]# (ρ= −0.62), Breslin [20] (d=0.91), Lee [27]# (coefficient$_{adjusted}$ −9.773)	Breslin [20]# (t: Mann–Whitney U=1.11–85.00, d= −0.54–0.58), Brooks [21], Lee [27]# (coefficient$_{adjusted}$ 6.515)									

Association estimates are listed where available. In cases where estimates were not available predictors were associated with SDB if the p-values did not cross the null hypothesis (p<0.05), or based on the author's reporting. AHI: apnoea–hypopnoea index; oAHI: obstructive AHI; CAI: central apnoea index; GORD: gastro-oesophageal reflux disease. #: in cases where authors are listed twice in different columns, different outcomes were assessed, details of which may be found in supplementary table A2.

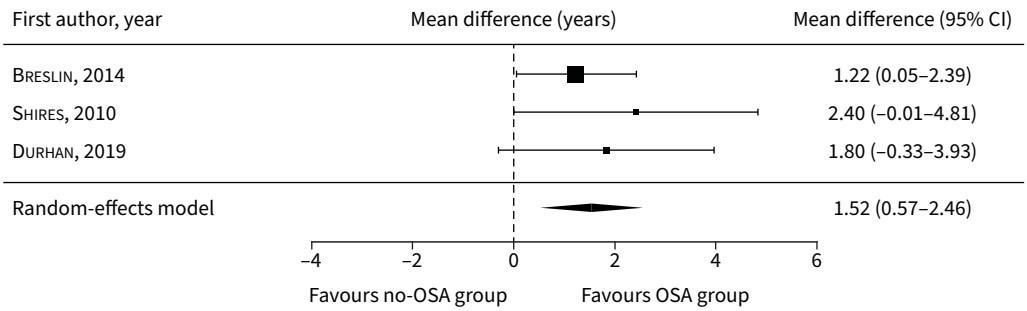

FIGURE 2 Meta-analysis of association of age with obstructive sleep apnoea (OSA).

Male sex

Overall, seven studies evaluated sex as a predictor for SDB in relation to the AHI [4, 20, 21, 29, 34, 35]. Five studies found a lack of association between sex and OSA [17, 20, 27, 34, 35]. Two prospective cohorts found associations between sex and OSA; in one, there was a predominance of females in the OSA group (AHI >5 events·h^{-1}) ($p<0.005$) and in the other, the frequency of OSA (AHI >3 events·h^{-1}) was higher in boys than in girls (63.7% *versus* 38.5%) [4, 21].

Two studies evaluated sex in relation to oAHI [29, 33]. Maris *et al.* [29] found that sex was not correlated with oAHI or presence of OSA, and Rosen *et al.* [33] found that there was no association between percentage of females and severity of OSA (when children where categorised as normal, mild OSA and moderate OSA).

There was one study that evaluated the relationship between sex and CAI. Naime *et al.* [30] did not find a correlation between sex and presence of CSA. However, when limiting the study population to just those >2 years, or those aged 3–10 years, females were more likely to have CSA [30]. There was no correlation between sex and presence of CSA in children aged ⩽2 years [30].

Meta-analysis of the association between sex and OSA

A total of six studies with cumulative 669 participants evaluating predictors of OSA (defined as AHI/oAHI >1–1.5 events·h^{-1}) were included in our meta-analysis (figure 3) [17, 20, 27, 33, 34, 35]. The pooled data identified that males were more likely to have OSA than females, although confidence intervals were wide (OR 1.33, 95% CI 0.96–1.83).

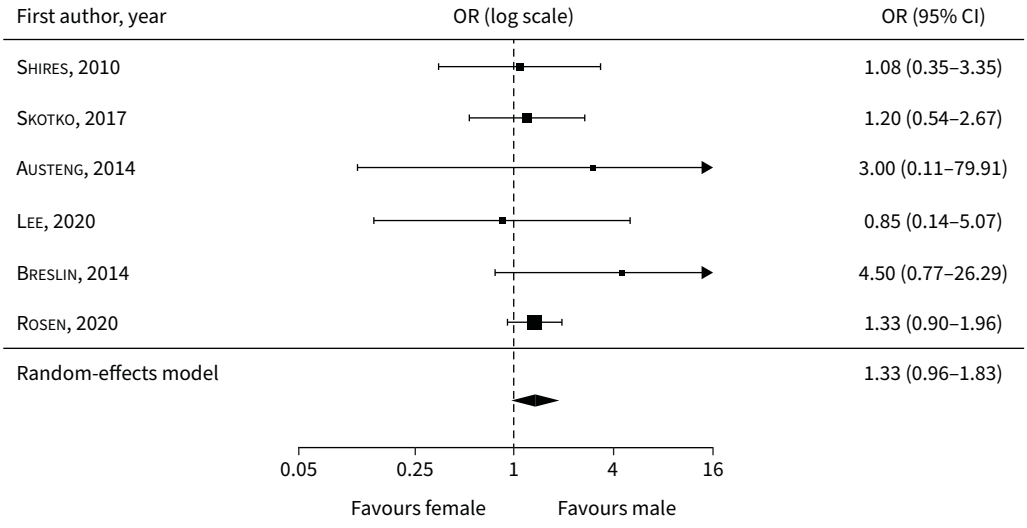

FIGURE 3 Meta-analysis of association of sex with obstructive sleep apnoea (OSA).

Body mass index

12 studies evaluated the relationship between body mass index (BMI) and AHI [4, 8, 9, 17, 19, 20, 21, 23, 24, 27, 34, 35]. Eight studies found no correlation between BMI and AHI [4, 8, 17, 20, 22, 23, 27, 35]. While BMI percentile was included in the final predictive model developed by Skotko *et al.* [35], it was not associated with AHI. Two studies found a positive association between BMI and AHI [9, 19]. Dyken *et al.* [9] reported a moderate positive correlation between AHI and BMI when evaluated continuously. A retrospective review by Basil *et al.* [19] reported an increase in the risk of OSA in individuals with obesity (defined as >95th percentile for BMI according to the Centers for Disease Control and Prevention (CDC) SAS height and weight z-scores) as well as an increase in the severity of OSA in these individuals. An additional two studies reported conflicting associations between BMI and OSA [24, 34]. Elsharkawi *et al.* [24] found a higher median AHI in those with obesity, as well as an increased likelihood of having a diagnosis of OSA. However, this study also reported very weak correlation between BMI percentile and AHI when evaluated continuously. Shires *et al.* [34] reported a positive association between age and mean BMI z-scores (CDC age- and sex-adjusted), but no association between AHI and absolute BMI. Furthermore, when evaluating females and males separately, there was no difference in the percentage of children with a BMI >50th percentile (according to the Swedish Down syndrome BMI chart used in this article) in the OSA group when compared to the group without OSA, in either sex [34].

Four studies commented on the relationship between BMI and oAHI [8, 19, 22, 29]. Two studies did not find any association between BMI and oAHI [8, 29]. Basil *et al.* [19] reported a weak correlation between BMI percentile and oAHI, when evaluated continuously using CDC SAS height and weight z-scores. Chamseddin *et al.* [22] reported no difference between mean oAHI of children with obesity compared to those without. However, when the study sample was dichotomised into children <12 years and ⩾12 years, children with obesity who were ⩾12 years had a higher mean oAHI than nonobese children. There was no difference detected in children <12 years. This study did not identify any difference in the overall prevalence of OSA in children with obesity compared to those without; however, there was an increased prevalence of severe OSA (oAHI ⩾10 events·h^{-1}) in children with obesity [22].

One study evaluated the relationship between BMI and nocturnal hypoventilation. Richard *et al.* [32] did not find a difference in median BMI between participants with nocturnal hypoventilation and those without.

Additional demographic characteristics

There were a limited number of studies (two or fewer) that did not identify any associations between the following factors and SDB: weight, height and race/ethnicity [4, 20, 21, 35].

Comorbidities

Gastrointestinal comorbidities

The presence of gastro-oesophageal reflux disease (GORD) was not correlated with either mean AHI or presence of OSA in two studies [8, 34].

The presence of GORD was found to be independently associated with a lower risk of oAHI >5 events·h^{-1} (OR 0.16, 95% CI 0.04–0.72) in a study by Nehme *et al.* [8].

Upper and lower respiratory comorbidities

A study by Nehme *et al.* [8] demonstrated an unclear association between asthma and an AHI >5 events·h^{-1} (OR 1.65, 95% CI 0.75–3.61) and rhinitis, rhinorrhea and sinusitis (considered together) and an AHI >5 events·h^{-1} (OR 2.13, 95% CI 0.90–5.04). When multivariate testing was performed, this comorbidity was still not predictive of an AHI >5 events·h^{-1} (OR 2.38, 95% CI 0.80–7.08) [8].

The presence of rhinitis, rhinorrhea and sinusitis (considered together) was not associated with an oAHI >5 events·h^{-1} (OR 2.22, 95% CI 0.92–5.37), but when multivariate testing was performed, this comorbidity was predictive of an oAHI >5 events·h^{-1} (OR 4.49, 95% CI 1.17–17.19) [8].

Additional comorbidities

There were a number of studies (three to four) which each evaluated a history of congenital cardiac abnormalities, adenoidectomy, tonsillectomy or adenotonsillectomy and found no association with SDB [4, 17, 20, 28, 31]. A limited number of studies (one to two) did not find an association between the following factors and SDB: developmental history including gestation at birth or failure to thrive, current or repaired cardiac abnormalities, psychiatric comorbidities, diabetes/metabolic syndrome, hypothyroidism, vocal cord paralysis, cleft lip/palate, pulmonary hypertension and scoliosis [8, 9, 25, 31].

Physical examination findings

Adenotonsillar hypertrophy

The relationship between adenotonsillar hypertrophy and AHI was evaluated in three studies [4, 8, 34]. Nehme [8] *et al.* reported that adenotonsillar hypertrophy was not predictive of an AHI >5 events·h^{-1} [8]. In contrast, Shires *et al.* [34] reported a strong positive correlation between tonsil size and AHI when evaluated continuously (r^2=0.75, p=0.002). Finally, de Miguel-Díez [4] *et al.* found that while patients with tonsillar hypertrophy were more likely to have a diagnosis of SDB (AHI >3 events·h^{-1}), adenoid hypertrophy was not associated with a diagnosis of SDB.

There were two studies which reported on the association between adenotonsillar hypertrophy and oAHI, both of which did not find a correlation [8, 29].

Dental examinations

Three studies evaluated the relationship between dental variables and AHI [4, 23, 35]. Only one study, by Durhan *et al.* [23], reported an association with dental examinations. This study identified an increase in the mean gingival index of children with OSA, when compared to those without. There was also an increase in the mean bleeding on probing of six sites per tooth in the group of children with OSA when compared to those without [23]. However, there was no association between decay, missing, filling and tooth scores and mean plaque index between subjects with OSA and those without [23].

Additional physical examination findings

There was one study that evaluated the presence of macroglossia and found no association with SDB [4].

Sleep behaviours

Parental questionnaires on sleep behaviours

Five studies evaluated the association between various parental questionnaires of sleep behaviours and AHI [8, 20, 21, 25, 35]. Two of these studies reported an association between increased parental reporting of sleep behaviours and AHI [25, 35]. In the predictive model developed by Skotko *et al.* [35], particular questions from the Children's Sleep Habits Questionnaire and Sleep-Related Breathing Disorder Questionnaire were found to be among the 15 most relevant predictive variables. The study concluded that parental responses on questionnaires related to sleep behaviours and SDB symptoms best discriminated patients with *versus* without OSA [35]. Nehme *et al.* [8] also reported that parental reporting of "struggling to breathe at night" correlated with presence of OSA. Friedman *et al.* [25] did not find an association between parental reports of frequency of night-time symptoms and presence of OSA. In addition, there was no difference in the distribution of OSA severity (categorised into normal, mild OSA, moderate OSA and severe OSA) between children with reported frequent and infrequent night-time symptoms [25].

Three studies reported on the association between parental questionnaires of sleep behaviours and oAHI; however, no correlations were identified [8, 21, 28].

Snoring

Snoring was evaluated as a predictor for SDB using AHI in a study by Banjar *et al.* [18], but was not found to be associated with either the frequency or the severity of respiratory disturbance.

Posada *et al.* [31] reported that snoring was able to predict OSA using oAHI with a sensitivity of 61.7%, a specificity of 100% and negative predictive value of 25%.

Additional sleep behaviours

One study did not find an association between the following symptoms and SDB: hours of sleep, sleep-efficiency or Epworth sleepiness scale scores [37].

Neuropsychological and developmental assessments

Parental questionnaires of neuropsychological or developmental functioning

Four studies evaluated the association between parental questionnaires of neuropsychological/developmental functioning and AHI [16, 20, 21, 27]. Two studies reported an association [27]. Lee *et al.*[27] reported higher age-adjusted Vineland Adaptive Behavior Scale II expressive communication scores in participants with OSA, when compared to those without. However, when the OSA group was limited to participants ages 6–12 years, there was no correlation [27]. Anand *et al.* [16] found a strong and moderate correlation between total and externalised behaviour scores of the Child Behavior Checklist and AHI, respectively, in children aged 3–5 years and 6–12 years. Additionally, a strong and moderate positive correlation was reported between Child Behavior Checklist ratings of attention in children aged 3–5 years and 6–12 years,

respectively. A moderate positive correlation was also found between internalising behaviour scores and AHI in children aged 3–5 years; however, this association was not reported in other age groups [16].

Cognitive function

Four studies reported on the association between cognitive function assessments and AHI [16, 20, 21, 27]. Anand *et al.* [16] reported a moderate inverse correlation between the development quotient and AHI when evaluated continuously. This study also found that higher severity of global development delay (as calculated by development quotient/intelligence quotient) was associated with higher AHI, on average [16]. Breslin *et al.* [20] reported a difference in verbal intelligence quotient between children with and without OSAS, where children in the OSA group scored nine points lower. There was also a decrease in the number of Cambridge Neuropsychological Test Automated Battery Intra-Extra Dimensional Set Shift changes completed by children with OSA compared to those without [20]. There was no difference in other measures of cognitive function [20]. Lee *et al.* [27] found that median age-adjusted NEPSY (Developmental Neuropsychological Assessment) scores were higher in participants with OSA compared to those without. Additionally, median age-adjusted Wechsler Preschool and Primary Scale of Intelligence vocabulary scores were not different in participants with OSA compared to those without [27]. However, when adjusted for age and full-scale intelligence quotient, the Wechsler Preschool and Primary Scale of Intelligence vocabulary scores were inversely associated with presence of OSA [27].

Miscellaneous

Urine metabolic markers

Two studies evaluated the use of urinary markers in predicting the presence of OSA using AHI [35, 24]. Elsharkawi *et al.* [24] reported that no individual biomarkers were able to predict OSA; however, the levels of four biomarkers considered aggregately were significant predictors of AHI >1 events·h^{-1}: decreased night-time norepinephrine, increased morning/evening norepinephrine, increased morning/evening dopamine and increased morning/evening taurine [24]. Elsharkawi *et al.* [24] also identified two biomarkers which were significant univariate predictors of moderate OSA: increased evening taurine and increased morning taurine. In the study by Skotko *et al.* [35], urine metabolic markers were not found to improve the positive or negative predictive value of a model to predict OSA [35].

Additional miscellaneous variables

There were a limited number of studies (one to two) which did not find an association between the following factors and OSA, as measured by AHI: parental income or education level, variables from lateral cephalograms, three-dimensional (3D) photographs or 3D anthropometric measurements [4, 8, 20, 21, 24–27, 29, 31, 35].

Discussion

To the best of our knowledge, this is the first review to systematically examine the literature for predictors of SDB in children with Down syndrome. Our review of the literature identified inconsistent associations between all clinical and biomarker predictors of SDB, despite a large number of studies. Associations were either inconsistent or not replicated in more than one study. A meta-analysis identified older age as being associated with OSA, but this was limited to evaluation of a small subset of studies. No clear sex predominance for OSA was identified on meta-analysis. Our findings further highlight the difficulty in predicting which children with Down syndrome have SDB from clinical evaluation. This is consistent with other studies that have attempted to identify individual clinical predictors of OSA.

When multiple predictors were considered simultaneously, this did not result in predictive ability sufficiently accurate to preclude objective testing [35]. The predictive model developed by Skotko *et al.* [35] included age, sex, race, Mallampati score, presence of macroglossia, neck circumference, Children's Sleep Habits Questionnaire and Sleep-Related Breathing Disorder Questionnaire questions, presence of thyroid disease/asthma/GORD and anthropometric measurements (BMI percentile, height percentile, weight percentile, sedentary blood pressure percentile, awake oxygen saturation measured by pulse oximetry) [35]. However, even when considering these factors together, Skotko *et al.*'s [35] model only had a negative predictive value of 73% and positive predictive values of 55% for detecting mild OSA.

On meta-analysis, consisting predominantly of children aged >4 years, it was identified that older age may be associated with increased OSA risk. This is consistent with findings from previous longitudinal studies identifying that OSA occurs across the paediatric age range [8]. This is possibly because OSA may recur, even when identified in young children [8]. Additionally, risk factors for OSA in children with Down syndrome may vary over time. While adenotonsillar hypertrophy is the predominant pathophysiological feature leading to SDB in young children, it is likely that other factors contribute to SDB in older children, including obesity and lingual tonsillar hypertrophy [38–40]. Young children with Down syndrome have

additional risk factors for OSA due to anatomic features including small oropharynx, narrow upper airway structure and mid-facial hypoplasia [41]. These anatomic features are maintained as they age, with the addition of new risk factors which include hypothyroidism and obesity [41]. This may account for the increased risk in older children, and the 90% prevalence of OSA in adults with Down syndrome [2].

Of note, our study did not investigate exclusively infant populations, which may have both different causes of SDB and normal values for apnoea and hypopnoea events [42, 43]. One study by Goffinski *et al.* [42] investigated predictors of OSA in infants aged ⩽6 months and found that the presence of dysphagia and congenital heart disease was the best predictor of OSA. This contrasts with our review, wherein only one of two studies reported an association between OSA and the presence of GORD and three studies reporting no association between congenital cardiac disease and OSA [4, 6, 20, 31, 34].

There was no identified sex predominance for OSA in children with Down syndrome in our systematic review. This is consistent with findings in the general population that there is equal sex prevalence in children before puberty [44]. However, post-puberty there is a male predominance in the general population [44]. This is thought to be due to several physiological differences that occur at puberty, including development of craniofacial sexual dimorphism and increase in sex hormones with subsequent effects on sleep and respiratory control [39]. Our meta-analysis of sex included all children aged <18 years, although statistically most fell into the pre-pubertal range. This probably accounts for the similar likelihood of OSA in males and females in our meta-analysis. Nonetheless, the relationship did trend towards males, which may be accounted for by the inclusion of some post-pubertal children.

Currently, the American Academy of Pediatrics guidelines recommend that all children with Down syndrome undergo a sleep study by the age of 4 years [10, 11]. Although this requirement is often difficult to fulfil due to limitations in resources and lengthy wait lists, our review supports the recommendation for routine screening of all children with Down syndrome [10]. Additionally, we suggest that longitudinal interval screening is needed throughout childhood. In particular, OSA may be even more common beyond the age of 4 years. As such, routine PSG screening beyond this age is needed so that SDB can be diagnosed and treated to prevent the long-term sequelae of SDB. The ideal frequency for longitudinal screening still needs to be determined.

Identification of biomarkers predicting SDB should continue to be a priority for future studies. Consensus regarding which PSG cut-offs for SDB are clinically relevant will help to improve the comparability of future studies aimed at identifying predictors of clinically relevant SDB. In the adolescent and adult population, where the prevalence reaches 90%, consensus PSG parameters for SDB will be particularly important for characterising severe disease and triaging resources appropriately [2]. This is vital, as the life expectancy of adults with Down syndrome continues to be low compared to the general population, possibly due to secondary consequences from diseases such as SDB [41, 45].

Limitations

Our review had several limitations. While all the included studies identified SDB using PSG, the gold-standard test for SDB diagnosis, studies used different cut-offs of AHI or oAHI to diagnose SDB. This may have affected the robustness of our data, as using different cut-points might alter the thresholds at which predictors are identified. Furthermore, while using multiple outcome measures of SDB (AHI/oAHI) increased the number of studies and predictors we were able to evaluate, thus increasing the generalisability of our findings, it also increased heterogeneity between studies, and made comparison challenging. Pooling studies that used AHI and/or oAHI to define OSA may have yielded less reliable estimates of associations between predictors and OSA, compared to using only one of these indices. Additionally, only two studies considered the presence of CSA or nocturnal hypoventilation, limiting the generalisability of our results to children with non-OSA SDB. Finally, while we considered predictors of any type of SDB, predictors may vary for different types of SDB and for infants under 2 years of age; this will need to be considered in future work.

Points for clinical practice

- This is the first review of predictors of SDB in children with Down syndrome. Several predictors were identified, although the evidence was contradictory.
- Meta-analysis identified that children with OSA were older than those without OSA.
- A lack of ability to predict OSA from clinical factors highlights the need for screening children with Down syndrome for SDB using PSG.
- Longitudinal screening is needed in children with Down syndrome, as SDB may present at older ages.

Conclusions

This review is the first to systematically summarise the literature on predictors of SDB in children with Down syndrome. We identified inconsistent associations between all clinical and biomarker predictors and presence of SDB. Our review confirms that SDB cannot be predicted from clinical markers and therefore supports the recommendation for routine screening of all children with Down syndrome for SDB using PSG. As our meta-analysis demonstrated that older age was associated with increased risk of OSA, there may be a need for longitudinal screening to diagnose children who may develop SDB as they get older.

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