Obstructive Sleep-Disordered Breathing in 2-18 Year Old Children: Diagnosis and Management

An ERS Statement

Task Force 2012-09

Online Supplementary Appendix

Previously published guidelines on the Diagnosis and Management of Obstructive SDB

Two major guidelines in English concerning the diagnosis and management of obstructive SDB have been published:

- The American Academy of Pediatrics revised Clinical Practice Guideline and the Technical Report on the Diagnosis and Management of uncomplicated childhood obstructive sleep apnoea syndrome (OSAS) in 2012 [1,2]. Children with complex abnormalities such as Down syndrome, craniofacial abnormalities or neuromuscular disorders, indications for treatment of OSAS and OSAS in infants are topics that have not been covered.
- The 2009 Royal College of Paediatrics and Child Health Report on Standards for Services for Children with Disorders of Sleep Physiology in Childhood includes only a brief discussion of OSAS in childhood [3].

Three guidelines on the methodology and/or indications of polysomnography have been published:

- The 1996 American Thoracic Society guideline for the indications, performance and scoring of polysomnography [4].
- The 2007 American Academy of Sleep Medicine (AASM) guidelines for the indications, performance, scoring and interpretation of polysomnography with an update version in 2012 [5,6].
- The 2011 American Academy of Sleep Medicine evidence-based review and practice parameters on respiratory indications for polysomnography in children [7,8].

However, full polysomnography is not a widely available diagnostic tool. In several centres around Europe, other modalities are also used for the objective diagnosis of obstructive SDB in childhood. Thus, there is clearly a need to summarise evidence for the diagnosis and management of obstructive SDB in settings with limited resources.

Unique characteristics of the ERS Document

The unique characteristics of the current document compared to previously published guidelines [2-6,8-10] are the following:

- it refers to all the severity spectrum of obstructive SDB from primary snoring to OSAS in children 2-18 years old

- it discusses conditions other than adenotonsillar hypertrophy and obesity which can predispose to obstructive SDB like craniofacial abnormalities and neuromuscular disorders
- it takes into account the available diagnostic facilities and accepted treatment policies in different European countries and describes diagnostic modalities that can be used as alternatives if polysomnography is not available
- it describes a step-by-step diagnostic and treatment approach.

Methodology used by the Task Force for Preparation of the ERS Document

The document contains a series of questions, formed by consensus of all members during two face-to-face meetings, with answers summarising the relevant literature. All answers have been incorporated into a stepwise management algorithm.

A systematic search of the literature was completed by the two chairs of the Task Force to answer the formulated questions. The MEDLINE, Scopus, Ovid, PsycINFO, EBSCO and CINAH Databases were searched for the period between January 1970 and December 2012. An additional search was performed from January 2013 until December 2014. Key words were: “adenoidectomy”; “adenoidal hypertrophy”; “adenotonsillar hypertrophy”; “polysomnography”; “sleep apnoea”; “sleep-disordered breathing”; “sleep-related breathing disorders”; “snoring”; “tonsillar hypertrophy”; “tonsillectomy”; “continuous positive airway pressure”; “non-invasive positive pressure ventilation”. The search was limited to articles in the English language and to humans aged 0-18 years. Articles on apnoea of prematurity were excluded.

In a first round of literature screening, members of the Task Force group screened all the retrieved titles and abstracts for relevancy. Articles on apnoea of prematurity, OSAS in adults or non-humans or not related to OSAS were excluded. Conference abstracts, letters and case reports were also excluded. In a second round of literature screening, the selected abstracts were distributed among all members by the two chairs of the Task Force. Each abstract was reviewed by one member who read the abstract and the full text if necessary and classified the abstract according to its relevance to one or more of the nine

broad topics of this document: definition of obstructive SDB; risk factors; pathophysiology; symptoms; diagnosis; morbidity; treatment; and treatment of SDB-related morbidity. During this round of literature screening, non-systematic reviews were excluded, whereas systematic reviews and meta-analyses were retained in the pool of articles.

In a third phase, questions were assigned to members of the Task Force randomly. Each question was assigned to two or more members who prepared an initial answer and a table summarising the evidence contained in the pool of articles. For this step, the methodological quality of the articles was graded as class I-IV according to the American Academy of Neurology Clinical Practice Guideline Process Manual [11]. Questions, answers (summary of the literature), literature review and evidence tables were consolidated in an initial draft document by the chairs of the Task Force. In a fifth phase, the document was discussed in detail during a third face-to-face meeting and all information was summarised in a step-by-step algorithm. The product of this meeting was circulated via the internet among all Task Force members for further suggestions and criticism and for checking the accuracy of evidence tables.

Topics for Future Research

Step 1. Recognition of the child at risk for obstructive SDB

What is not known?

- It is unclear whether the relationship between severity of OSAS and degree of adiposity changes with age.
- The clinical indications of MRI or CT of the upper airway have not been defined.
- Prospective studies based on polysomnography are necessary to explore the effect of premature birth on OSAS risk and to identify potentially reversible pathogenetic mechanisms.
- Familial characteristics which predispose to SDB have not been studied in detail.

Step 2. Recognition of morbidity and conditions frequently co-existing with SDB

What is not known?

- The interactive effect of SDB, individual vulnerability and environmental factors on the development of cognitive and academic deficits in children with OSAS has not been determined.
- The cumulative effect of attention-deficit, hyperactivity disorder and genetic factors on the development of behavioural disorders and emotional lability in children with OSAS.
- Pathophysiologic mechanisms linking OSAS and enuresis have not been studied adequately.
- Subgroups of children with OSAS who are at risk of growth failure have not been defined.
- It is unclear whether adenotonsillectomy for OSAS improves recurrent wheezing and oral-motor dysfunction

Step 3. Recognition of factors predicting long-term persistence of obstructive SDB

What is not known?

- How to calculate individualised risk of persistent OSAS if no treatment is implemented.

Step 4. Objective diagnosis and assessment of obstructive SDB severity

What is not known?

- There are no studies on the prevalence of primary snoring, upper airway resistance syndrome and obstructive hypoventilation in childhood.
- The clinical importance of differentiating primary snoring from upper airway resistance syndrome is unclear.

The pulse transit time and Sleep Clinical Record should be validated in multicentre studies.

Step 5: Indications for treatment of obstructive SDB

What is not known?

- How early SDB should be treated to avoid irreversible OSAS-related neuronal damage and what is the impact of confounding factors such as age, environment, race, obesity on neurodevelopmental outcomes?
- Should children with primary snoring be treated?

Step 6: Stepwise treatment approach for obstructive SDB

What is not known?

- There are no well-designed studies supporting a stepwise approach to the management of OSAS in childhood.
- Evidence on the short- and long-term efficacy of weight loss and use of antiinflammatory medications is limited.
- It is unknown whether isolated adenoidectomy, tonsillectomy and partial tonsillectomy are equally effective to adenotonsillectomy.
- The efficacy of craniofacial surgery in children with OSAS and syndromic or non-syndromic craniofacial abnormalities has not beed studied in randomised, controlled trials using upper airway imaging and polysomnography.

Step 7: Recognition and management of persistent SDB

What is not known?

- How can nasopharyngoscopy, drug-induced sleep endoscopy and MRI of the upper airway be used to determine the best sequence of treatment interventions in children with persistent OSAS after adenotonsillectomy?

Online Supplementary Tables

Online Supplementary Table 1.

Step 1: Recognition of the child at risk for obstructive SDB

Question 1.1. Which symptoms reported by parents are directly related to intermittent upper airway obstruction?				
Author, year	**Type of Study**	**Class**	**Subjects**	**Methods and findings**
Goodwin et al, 2005 [12]	Population-based, cross-sectional study	IV	480 children from the community (6-11 y.o.)	Frequent loud snoring was associated with 3.6 times increased risk of respiratory disturbance index ≥ 1 episode/h
Brunetti et al, 2001 [13]	Population-based, cross-sectional study	IV	895 children from the community (mean age 7.3 years; range 3-11 years)	Children were screened by a self-administered questionnaire. All children with habitual snoring underwent a screening sleep study at home, and those with an oxygen desaturation index > 2 episodes/h were considered for nocturnal polygraphic monitoring. Children with AHI > 3 episodes/h were diagnosed with OSA; 79.3% of children were non-snorers, 15.8% were occasional snorers, and 4.9% were habitual snorers. The prevalence of OSAS was 1.8% (95% CI, 1.6 to 2.0). Snoring, reported apnea, troubled sleep, nocturnal sweating, and oral breathing were more frequently present in subjects with OSAS compared to those without.

Question 1.2. Which findings on physical examination are associated with obstructive SDB?				
a. *Tonsillar size*				
Author, year	**Type of Study**	**Class**	**Subjects**	**Methods and findings**
Mitchell et al, 2015 [14]	Multicentre, single-blind, randomised, controlled trial	I	464 children (5-9 y.o.) with OSAS randomly assigned to early adenotonsillectomy (median baseline obstructive AHI 4.8 episodes/h) or watchful waiting (median baseline obstructive AHI 4.5 episodes/h). OSAS was defined as an obstructive AHI ≥2 episodes/h or an obstructive apnea index ≥1 episode/h.	Baseline data were analysed. Multivariable analysis models were used to identify significant predictors of the AHI and the oxygen desaturation index (ODI). African American Race, obesity (body mass index z score > 2), and the Pediatric Sleep Questionnaire (PSQ) total score were associated with higher levels of AHI and ODI (P = .05). However, they explained less than 3% of the variance in OSAS severity. Tonsillar size and Friedman palate position were not associated with increased AHI or ODI.
Papaioannou et al, 2013 [15]	Cross-sectional study	IV	149 children without snoring (aged 0-15.9 years) and 33 children with snoring (aged 1.6-15 years) who underwent MRI	In children without snoring, adenoid size increased during the first 7-8 years of life and then progressively decreases.

			of the head for diagnostic purposes	Size of the nasopharyngeal airway lumen increases slowly up to age 8 years and rapidly thereafter. Similar patterns were noted for the tonsils and oropharyngeal airway. In children with snoring, adenoid and tonsils were large irrespective of age, and nasopharyngeal airway size increased slowly with age.
Nolan & Brietzke, 2011[16]	Systematic review of 20 studies	-	3353 subjects; mean age 6.7 years; age range 2.7-11.7 years; mean sample size of included studies was 161.	Eleven of 20 studies found a significant association between subjective tonsil size and objective OSAS, whereas 9 did not find such an association. Studies demonstrating a significant association were of lower methodologic quality when compared to those not supporting tonsillar hypertrophy as a risk factor for OSAS.
Howard & Brietzke, 2009 [17]	Prospective cohort study	IV	34 subjects with age 2-9 years	Objective tonsil size correlates with objective tonsil weight. Multivariate regression analysis revealed that objectively measured tonsil weight obtained after tonsillectomy was the most robust predictor of preoperative AHI (p=0.003) next to age and hard palate length. Friedman/Mallampati palate position was not related to AHI.
b. *Allergic rhinitis, nasal septum deviation, nasal turbinate hypertrophy*				
Author, year	**Type of Study**	**Class**	**Subjects**	**Methods and findings**
Greenfeld et al, 2013 [18]	Retrospective cohort	IV	2178 children and adolescents (65% boys; mean age 4.9 ± 3.5 years; range 3 months–18 years).	18% of patients had a history of asthma/ atopy. Mean obstructive AHI in the winter was significantly higher than in the summer (9.1 ± 9.6 episodes/h vs 7.5 ± 7.0 episodes/h; P = 0.01), and especially in children ≤5 y.o. (10.2 ± 10.5 episodes/h vs 7.9 ± 7.3 episodes/h; P = 0.008). Asthma/atopy had no significant effect on seasonal variability.
Lin et al, 2013[19]	Systematic review	-	27015	18 studies of low methodologic quality were analyzed with 12 of them supporting an association of allergic rhinitis with SDB. In 7 studies, skin-prick testing or in vitro measurement of specific IgE to common environmental allergens was carried out, but in 4 of these 7 studies there was no report of nasal symptoms that would allow diagnosis of allergic rhinitis and not only demonstration of allergic sensitization. Six studies used OSAS-

				the most severe form of SDB-as an outcome measure, whereas in the remaining articles snoring-a symptom of SDB-was recorded.
Corbo et al, 2001[20]	Cross-sectional	IV	2209 children, 10-15 y.o.	Nasal septum deviation is a risk factor for habitual snoring (snoring often): OR 2.75 (1.3-5.9)
Sullivan et al, 2008 [21]	Retrospective	IV	500 children diagnosed with SDB (6.2 ± 1.2 y.o.); 441 patients underwent adenotonsillectomy; in 75 children with inferior nasal turbinate hypertrophy reduction of the turbinates was recommended.	In children with inferior nasal turbinate hypetrophy and SDB, posttreatment AHI was significantly lower in those who underwent both adenotonsillectomy and radiofrequency treatment of the inferior turbinates (n=27) compared to subjects who had adenotonsillectomy alone (AHI 1.9 ± 2.2 episodes/ h vs. 3.5 ± 2.1 episodes/h, respectively, P <0.05)
Bixler et al, 2009 [22]	Cross-sectional cohort study	I	700 children randomly selected from 5740 children whose parents had fiiled in questionnaires. Age range was 5-12 years	Participants underwent nocturnal polysomnography and nose and throat examination by an ENT specialist. Nasal abnormalities (nasal drainage, chronic sinusitis/rhinitis and turbinate hypertrophy were risk factors for mild SDB 1 ≤ AHI <5 episodes/h but not for moderate-to-severe OSAS.
c. *Obesity*				
Author, year	**Type of Study**	**Class**	**Subjects**	**Methods and findings**
Alonso-Alvarez et al, 2014 [23]	Cross-sectional, multicenter study	IV	248 obese children (BMI ≥ 95th percentile for age and sex; 54.4% males) with mean age 10.8 ± 2.6 years (range 3-14 years) and mean BMI 28.0 ± 4.7 kg/m^2 (96.8 ± 0.6 percentile) were randomly selected from primary care centers	The Pediatric Sleep Questionnaire (PSQ) was completed and nasopharyngoscopy and polysomnography were performed. Choanal obstruction by adenoidal hypertrophy was classified using nasopharyngoscopy: 75–100%, 50–75%, 25–50%, 0–25%. The mean respiratory disturbance index, obstructive respiratory disturbance index, and obstructive AHI were 5.58 ± 9.90 episodes/h, 5.06 ± 9.57 episodes/h, and 3.39 ± 8.78 episodes/h, respectively. The prevalence of OSAS ranged from 21.5% to 39.5% if obstructive AHI, obstructive respiratory disturbance index, or respiratory disturbance index ≥ 3 episodes/h were used as cut-off values. In the multivariate logistic regression analysis OSAS was included as an outcome measure and age, gender, tonsillar hypertrophy, adenoidal

				hypertrophy, obesity, the interaction between tonsillar hypertrophy and BMI z-score and the interaction between tonsillar hypertrophy and adenoid hypertrophy as independent variables.. Only the degree of tonsillar hypertrophy and adenoid hypertrophy were significant predictors in the model.
Kohler et al, 2008 [24]	Retrospective cohort study	IV	190 children (4-12 y.o.) with snoring who were referred for evaluation of upper airway obstruction	Children had nocturnal polysomnography and they were classified as infrequent snorers (n = 80), habitual snorers (n = 68) or patients with OSAS (n = 42) if obstructive AHI ≥1 episode/h. 35% of children were overweight or obese and body mass index was a significant but weak predictor of obstructive AHI.
Xu et al., 2008 [25]	Prospective cohort study	II	99 obese children and 99 control subjects of normal weight who were recruited from specialty clinics	Standardized questionnaires were completed, and children had physical examination, lateral neck X-ray, polysomnography and arterial blood gas analysis. Obesity was defined as body mass index z-score >1.96 and adenoidal hypertrophy as adenoidal/nasopharygeal ratio >0.67. OSAS was defined as an AHI) > 5 episodes/h or obstructive apnea index > 1 episode/h. Obese patients had significantly higher AHI and obstructive apnea index, and lower minimum arterial oxygen saturation than control subjects. The prevalence of OSAS was significantly higher in obese children than in nonobese participants. Obesity, tonsillar hypertrophy, and adenoid hypertrophy were independent risk factors for OSAS ($P < 0.05$). There was a positive correlation between body mass index z-score and AHI ($r = 0.535$; $P < 0.001$), and an inverse correlation between obesity and ohygen saturation of hemoglobin nadir ($r = -0.507$; $P < 0.001$). End-tidal CO_2, P_aCO_2 and bicarbonate levels were within the normal range.
Beebe et al, 2007 [26]	Prospective cohort study	III	60 children (10-16.9 y.o.) from a weight-management clinic; 22 healthy controls	Sixty children aged 10-Actigraphy, polysomnography, and parent- and self-report questionnaire were employed. Overweight participants had more symptoms of SDB, later sleep onset,

				shorter sleep duration, and more disrupted sleep than controls. Parents of overweight participants, reported more frequently daytime sleepiness, parasomnias, and inadequate sleep as compared to controls. Group differences in academic grades and depressive symptoms were at least partially accounted for by short sleep and daytime sleepiness. AHI was 2.17 ± 3.08 episodes/h vs 0.59 ± 1.11 episodes/h in obese vs. non-obese children. 13% of the obese children had an AHI >5 episodes/h and 50% had an AHI > 1 episode/h, whereas 0% of 22 normal weight controls had an AHI > 5 episodes/h and 14% had an AHI > 1 episode/h. AHI was 2.2 ± 3 episodes/h vs 0.6 ± 1.1 episodes/h in obese vs. non-obese children (P=0.001).
Verhulst et al, 2007 [27]	Cross-sectional study	IV	27 overweight and 64 obese subject (40 boys; mean age 11.2 ± 2.6 years).	All participants underwent nocturnal polysomnography. OSAS was defined as obstructive apnea index ≥ 1 episode/h or obstructive AHI ≥ 2 episodes/h; mild OSAS: 2 ≤ AHI <5; moderate-to-severe OSAS: AHI ≥5). Primary snoring was diagnosed when snoring was detected by microphone but without abnormalities in polysomnography. 53% of participants were normal, 11% had primary snoring, 11% had mild OSAS, 8% had moderate-to-severe OSAS and 17% had central sleep apnea. Only enlarged tonsils significantly predicted moderate-to-severe OSAS.
Goodwin et al, 2003 [28]	Population-based, cross-sectional study	IV	239 children (6-11 y.o.; 55.2% boys; 51% Hispanic)	Home polysomnography was performed. Hispanic or Caucasian ethnicity, sex, age, obesity, insomnia, and witnessed apnea were not associated with respiratory disturbance index.
Wing et al, 2003 [29]	Cross-sectional study	IV	46 obese children (10.8 ± 2.3 y.o.; body mass index 27.4 ± 5.1); 44 sex- and age-matched normal weight children (11.7 ± 2.1 y.o.; body mass index 18 ± 1.8)	Depending on the criteria used, 26% or 32.6% of obese children had SDB; 2.3% of normal controls had obstructive apnea index ≥1 episode/h and 4.5% had respiratory disturbance index ≥5 episodes/h. Presence of SDB was related to tonsillar hypertrophy (size >2) (OR 12.67; 95% CI 2.14-75.17) and BMI (OR 1.20; 95% CI 1.08-1.33).

Chay et al, 2000 [30]	Cross-sectional, population-based study	IV	3,671 obese school children were screened for OSAS by questionnaire. 146 obese children and symptoms of OSAS underwent polysomnography.	26 children had AHI >5 episodes/h (overall prevalence 0.7%). The prevalence of OSAS (13.3%) was higher in morbidly obese (≥180% ideal body weight) than in less obese children (<180% ideal body weight).
Redline et al, 1999 [31]	Population-based, cross-sectional study	IV	399 children and adolescents (2-18 y.o.), recruited as members of families with a member (a proband) with diagnosed sleep apnea (31 index families) or as members of neighborhood control families (30 families).	Participants were evaluated by home nocturnal multichannel monitoring and SDB was defined as an AHI ≥10 episodes/h (moderate severity SDB) or < 5 episodes/h (no SDB). SDB of moderate severity was significantly associated with obesity (OR 4.59; 95% CI 1.58-13.33) and African-American race (odds ratio, 3.49; 95% CI, 1.56 to 8.32).
Mallory et al, 1989 [32]	Cross-sectional study	IV	41 children and adolescents (mean age 10.3 ± 4.4 years) with history of breathing difficulty-snoring during sleep and morbid obesity (208 ± 42.2% ideal body weight)	All subjects underwent polysomnography. The polysomnograms in 37% (15/41) of the patients were abnormal because of apnea, hypopnea, excessive arousals, or gas exchange abnormalities. Multivariable analysis demonstrated no significant association between weight, age, or gender and any parameters on the polysomnogram.
d. *Retrusive chin, steep mandibular plane, vertical direction of craniofacial growth and a tendency towards class II malocclusion in non-syndromic children*				
Author, year	**Type of Study**	**Class**	**Subjects**	**Methods and findings**
Flores-Mir et al, 2013 [33]	Meta-analysis	-	8 studies that employed polysomnography to diagnose OSAS were used in the meta-analysis; studies with syndromic participants or participants receiving orthodontic and/or orthognathic treatment were excluded	Three of the evaluated cephalometric variables (angle from sella-nasion line to A point, angle from sella-nasion line to B point and angle from A point to nasion point to B point) had statistically significant differences compared to control subjects. Results of the meta-analysis should be considered cautiously due to the limited number of cephalometric variables that were analyzed. Dentists who identify patients with a craniofacial morphology consistent with OSAS (retrusive chin, steep mandibular plane, vertical direction of growth and a tendency toward Class II malocclusion) should inquire about symptoms of SDB.
Katyal et al, 2013 [34]	Systematic review and meta-analysis	-	9 studies were included in the systematic review and 6 in the meta-analysis (case-control trials, or cohort studies including controls and non-	Compared to controls, children with OSAS and primary snoring had increased weighted mean differences in the difference of the angle sella-nasion-

			syndromic children 0-18 y.o. with SDB diagnosed by a screening questionnaire or polysomnography).	A-point and the angle sella-nasion-B-point (1.64 degrees and 1.54 degrees, respectively; P <0.001). This finding is due to mandibular retrusion in children with primary snoring but not in children with OSAS. The small statistically significant differences between children with SDB and controls are of marginal clinical significance.
e. *Midface deficiency (Apert syndrome, Crouzon syndrome, Pfeiffer syndrome, unrepaired or repaired cleft palate) and marked mandibular hypoplasia (Pierre Robin sequence, Treacher-Collins syndrome, Nager syndrome, Stickler syndrome, juvenile idiopathic arthritis)*				
Author, year	**Type of Study**	**Class**	**Subjects**	**Methods and findings**
Akre et al, 2012 [35]	Prospective cohort study	IV	19 Norwegian patients with Treacher Collins syndrome (≥5 y.o.)	18 of 19 participants had OSAS based on polysomnography. Subjectively evaluated snoring did not predict OSAS. There was no significant association between the severity of Treacher Collins syndrome and the OSAS severity.
Robison et al, 2011 [36]	Retrospective, cohort study	IV	459 patients with nonsyndromic cleft palate and 48 additional patients with Pierre Robin syndrome	OSAS symptoms and polysomnography results were reviewed. 172 of the 459 (37.5%) patients had symptoms of SDB and 39 (8.5%) had OSAS. 89 (51.7%) of patients with SDB/OSAS were subjected to surgical intervention (mostly adenotonsillectomy). 35 of 48 (72.9%) patients with Pierre Robin syndrome had symptoms of SDB and/or OSAS.
de Jong et al, 2010 [37]	Retrospective cohort study	IV	167 children with Apert, Crouzon, Pfeiffer, Muenke or Saethre-Chotzen syndrome (1-25 y. o.; at time of referral age of 1 years and 2 months to 10 years and 3 months)	31% of subjects with Apert syndrome and 27% of subjects with Crouzon/Pfeiffer syndromes had OSAS
Cloonan et al, 2009 [38]	Retrospective cohort study	IV	124 children with hemifacial microsomia and 349 control subjects	The Pediatric Sleep Questionnaire (PSQ) was completed by parents. Snoring was more frequently present in children with hemifacial microsomia (29%) than in controls (17%). Compared to controls children with hemifacial microsomia had 1.9 times more frequently symptoms on the PSQ breathing scale and 1.3 times more frequently symptoms on the PSQ sleepiness scale. Also children with hemifacial microsomia had 1.4 times more frequently night awakenings compared to controls.

MacLean et al, 2009 [39]	Cross-sectional study	IV	248 children (mean age 33.4 months; 0-5 y.o.) with cleft lip and/or palate	Questionnaires were completed by parents/guardians. OSAS was demonstrated in 31.4% of the children. The three most frequent symptoms were heavy or loud breathing, easily distracted, and on the go or driven by a motor. Age, cleft classification and surgical status did not increase the risk of OSAS.
Mac Lean et al, 2008 [40]	Retrospective cohort study	IV	Retrospective review of clinical records and 99 sleep studies from 62 children with cleft palate	Group of children with cleft palate and features associated with SDB. 87% of children had OSAS and 28% of children with SDB had severe disease.
Pijpers et al, 2004 [41]	Retrospective cohort study	IV	Data of 72 children with Apert (n=28), Crouzon (n=30), or Pfeiffer syndrome (n=14) were analyzed retrospectively (mean age 9.3 years; range 0-17 years).	Data were collected from the medical records and a questionnaire was mailed to caregivers. Based on the medical records 26% of the children had potential OSAS compared to 53% based on the questionnaire. Severity and presentation of OSAS were not related to the child's age. OSAS symptoms were present in almost 50% of the children during upper respiratory infections. Treatment interventions included adenotonsillectomy, continuous positive airway pressure, and Le Fort III operation.
Rose et al, 2002 [42]	Retrospective cohort study	II	43 children with cleft palate (mean age 12.1 ± 3.8 years) and 20 control children matched for age, sex, and body mass index.	None of the patients with cleft palate had apparent symptoms of SDB. Children with cleft palate had significantly higher respiratory disturbance index and snoring index, but no increased apnea index.
f. *Neuromuscular disorders (cerebral palsy, Duchenne muscular dystrophy, myotonic muscular dystrophy) and uncontrolled epilepsy*				
Author, year	**Type of Study**	**Class**	**Subjects**	**Methods and findings**
Jain et al, 2013 [43]	Retrospective, cohort study	IV	60 children with epilepsy and suspected SDB: 45 with OSAS (10.3 ± 6.9 y.o.) and 15 with primary snoring (8.4 ± 3.5 y.o.)	Uncontrolled epilepsy was a risk factor for OSAS (P = 0.02). Obstructive apnea index increased with increasing number of antiepileptic drugs.
Miano et al, 2013 [44]	Prospective, cohort study	IV	298 children with OSAS (obstructive AHI >1 episode/h) and mean age 5.75 ± 3.17 years (186 males; mean BMI percentile 69.86 ± 33.74)	42.3% had tonsillar hypertrophy; 42.6% had narrow palate; mean AHI was 6.04 ± 9.73 episodes/h and mean overnight SpO_2 97.06 ± 1.52%. Children were recruited prospectively and underwent their first video-polysomnography (video-PSG) for SDB in a teaching hospital sleep center. 48 of the 298

				children (16.1%) had interictal epileptiform discharges and 3 of 48 children had nocturnal seizures (2 with rolandic epilepsy; and 1 with frontal lobe epilepsy). 11 of 48 subjects with interictal epileptiform discharges had repeat polysomnography after 6 months and in 6 of the 11 subjects the discharges disappeared and the AHI decreased. 38 subjects without interictal epileptiform discharges underwent repeat polysomnography 6 months later and in 4 of them, there were numerous stereotyped movements during sleep and they were diagnosed with nocturnal frontal lobe epilepsy.
Pinard et al, 2012 [45]	Retrospective, cohort study	IV	20 children with congenital muscular dystrophies, aged 4-17 years	Overnight polysomnography was performed. Compared to healthy controls, children with congenital muscular dystrophies had frequent awakenings, decreased total sleep time and REM sleep duration. AHI was >10 episodes/h in 3 patients and 5-10 in 4 patients.
Suresh et al, 2005 [46]	Retrospective, cohort study	IV	34 children with Duchenne muscular dystrophy aged 1-15 years	22 (64%) children had symptoms of SDB and 32 subjects underwent polysomnography. 10 patients had OSAS and 11 subjects had sleep hypoventilation. OSAS presents in the first decade of life, and sleep hypoventilation at the beginning of the second decade. Presence or absence of diurnal or nocturnal symptoms did not predict or excluded SDB.
Mellies et al, 2003 [47]	Retrospective, cohort study	IV	49 children with neuromuscular disorders aged 5-18 years	71% of patients had SDB and 49% had SDB with nocturnal hypoventilation. Inspiratory vital capacity < 60% predicted SDB and < 40% predicted SDB with nocturnal hypoventilation.
Barbe et al, 1994 [48]	Retrospective, cohort study	IV	6 patients with Duchenne muscular dystrophy aged 12-22 years	Mean AHI was 11 ± 6 episodes/h. Severity of daytime symptoms correlated with AHI. Most apneas were central and occurred mainly during REM sleep.
Khan et al, 1994 [49]	Retrospective, cohort study	III	21 participants (13-23 y.o.) with Duchenne muscular dystrophy nonambutant and 12 age-matched healthy controls	13 of 21 patients had SpO_2 drops <90% during sleep, and in 12 of the 13 participants episodes of desaturation accompanied apneas; 60% of the

				recorded apneas were obstructive. The older the patients, the longer the sleep period with hypoxemia. 62% of subjects had nocturnal oxygen desaturation of hemoglobin and 50% had respiratory events during REM sleep.
Kotagal et al, 1994 [50]	Retrospective, cohort study	III	9 patients with spastic quadriparesis (mean age 36.7 months) and 9 age-matched controls (mean age 37.4 months).	5 of 9 patients had OSAS.
g. *Achondroplasia, Chiari malformation, Down syndrome, Ehlers-Danlos syndrome, mucopolysaccharidoses, Prader-Willi syndrome*				
Achondroplasia				
Author, year	**Type of Study**	**Class**	**Subjects**	**Methods and findings**
Afsharpaiman et al, 2011 [51]	Retrospective cohort study	IV	46 children with achondroplasia aged 3 months-14 years	25 of 46 (54.3%) patients had OSAS (AHI >5 episodes/h). The follow-up period for 19 of 46 children was 3 months-11 years. 13 patients underwent adenotonsillectomy and 9 required CPAP.
Ednick et al, 2009 [52]	Retrospective, cohort study	III	24 infants (12 infants with achondroplasia; 12 age- and sex-matched controls).	All infants underwent polysomnography brain MRI. Infants with achondroplasia had a significant increase in respiratory disturbance index and decrease in spontaneous and respiratory arousal indices. Patients with achondroplasia had smaller size of the foramen magnum size, but there were no significant correlation with the respiratory disturbance index.
Sisk et al, 1999 [53]	Retrospective, cohort study	IV	95 children with achondroplasia aged 1 day to 14 years	OSAS was diagnosed clinically in 36 children (38%). Polysomnography was completed in some of them. Adenotonsillectomy was performed in 22 patients, and 18% of them required further treatment . 10 patients underwent adenoidectomy and 90% of them required further surgery for recurrent OSAS. 2 children had tonsillectomy only and one of them required additional adenoidectomy.
Mogayzel et al, 1998 [54]	Retrospective, cohort study	IV	88 children with achondroplasia (1 month- 12.6 years old)	5 children had history of tracheostomy and 7 children were receiving supplemental oxygen prior to polysomnography. 47.7% of subjects had abnormal polysomnography. Median obstructive apnea index was 0 (0- 19.2 episodes/h) and median number of central apneas with desaturation was

				0.5 (0-49 episodes/h). The median SpO_2 nadir was 91% (50-99%), and the median peak end-tidal pCO2 was 47 mm Hg (36-87 mm Hg). 2 additional children were treated with CPAP, and 3 additional subjects underwent tracheostomy.
Tasker et al, 1998 [55]	Prospective, cohort study	IV	17 infants (3 girls) with respiratory symptoms before 1 year of age	Group 1 infants (n = 6) had only OSAS. Group 2 (n = 6) had OSAS and hydrocephalus with a small foramen magnum. Group 3 (n = 5) had OSAS and cor pulmonale and 3 of them died due to cardiorespiratory failure. All children had a a small foramen magnum and moderately-to-severe gastroesophageal reflux.
Waters et al, 1993 [56]	Retrospective, cohort study	IV	20 patients with achondroplasia (15 children aged 1 to 14 years; 5 young adults, aged 20 to 31 years)	All subjects underwent polysomnography. All of them had upper airway obstruction and 15 (75%) participants had apnea index >5 episodes/h. Partial upper airway obstruction and central apneas were also recorded.
Chiari malformation				
Dhamija et al, 2013 [57]	Retrospective, cohort study	IV	24 children (median age 6 years) with Chiari malformation type I	16 subjects had perimedullary subarachnoid space effacement (effaced group) on MRI and the remaining children did not have effacement. The central apnea index in the former [median 1.5 episodes/h (interquartile range 1-3.5) was significantly higher than in the latter [0.5 episodes/h (0-1.5)]. Cortical arousal index was also significantly higher in the effaced group than in the non-effaced group. Greater descent of tonsils was associated with significantly higher central apnea index, total arousal index and respiratory arousal index.
Khatwa et al, 2013 [58]	Retrospective, cohort study	IV	22 children with Chiari malformation type I (11 males median age 10 years, range 1-18 years)	3 children had central sleep apnea, 5 had OSAS and one child had both obstructive and central sleep apneas. Children with SDB had excessive crowding of the brainstem structures at the foramen magnum and greater length of herniation relative to children without SDB. Patients with central sleep apneas underwent surgical decompression, with improvement in polysomnography.

Losurdo et al, 2013 [59]	Prospective, cohort study	III	53 children and adolescents with Chiari malformation type I (27 females; mean age 10.3 ± 4.3 and range 3-18 years).	13 patients had SDB on polysomnography. Patients with SDB, compared to those without SDB, had higher prevalence of hydrocephalus, syringomyelia and neurological symptoms. There were no differences in age, gender, frequency of epilepsy, and size of the herniation on MRI. Obstructive SDB was associated with syringomyelia and central SDB was related to hydrocephalus.
Alsaadi et al, 2012 [60]	Retrospective, cohort study	IV	16 children (11 boys; mean age 4.7 years; range, 0.8-10 years) with Chiari II malformation	Overnight polysomnography was performed. Mean AHI was 6.3 episodes/h (range 0.2-24.5 episodes/h). The mean central apnea-hypopnea index was 5.9 episodes/h (range 0-24.5 episodes/h) and the mean obstructive AHI was 0.4 episodes/h (range 0-2.9 episodes/h).
Down syndrome				
Fung et al, 2012 [61]	Case-control study	III	Over a period of 4.5 years, 23 children with Down syndrome (7 girls; mean age 7.09 ± 4.37 years) and persistent snoring or SDB; 23 matched controls for age, gender, and BMI-percentile (mean age 7.6 ± 4.14 years).	Children underwent sleep nasopharyngoscopy under intravenous sedation. Children with Down syndrome had more frequently pharyngeal or lingual collapse than the controls. The two groups did not differ regarding frequency of tonsillar hypertrophy.
Shott et al, 2006 [62]	Prospective, cohort study	IV	56 children with Down syndrome over a 5-year period	Children underwent polysomnography at a mean age of 42 months (4-63 months). A questionnaire on sleep patterns was completed by parents. Abnormal polysomnography was defined as obstructive index >1episode/h or carbon dioxide level >45 mm Hg for >2/3 of the study or >50 mm Hg for >10% of the study, and/or unexpected SpO_2 <92% during sleep or repeated intermittent desaturations <90%. 57% of children had OSAS but of the parents who reported abnormal sleep patterns only 36% had abnormal polysomnography.
de Miguel-Diez et al, 2003 [63]	Cross-sectional study	IV	108 children with Down syndrome (mean age 7.9 ± 4.5 years; range, 1-18 years) irrespective of clinical features of SDB.	All children underwent nocturnal cardiorespiratory polygraphy. SDB was defined as AHI ≥3 episodes/h. In multivariate analysis, age <8 y.o. (OR 3.36; 95% CI 1.40-8.06); male gender (OR 3.32; 95% CI 1.32-8.12); and

				tonsillar hyperplasia (OR, 5.24; 95% CI 1.52-19.03) were significantly associated with SDB. BMI, adenoid hyperplasia, previous tonsillectomy or adenoidectomy, congenital heart disease, malocclusion or macroglossia did not affect SDB frequency.
Dyken et al, 2003 [64]	Cross-sectional study	IV	9 boys and 10 girls with Down syndrome	Children underwent overnight polysomnography. Frequency of OSAS was 79% (95% CI 54%-94%), and the median apnea index was 3 episodes/h per hour (interquartile range, 2-5 episodes/h), median AHI 6 episodes/h (interquartile range 3-8 episdoes/h) and median SpO_2 nadir was 88% (interquartile range 84%-90%). Higher BMI was significantly associated with higher AHI and lower SpO_2 nadir; there was a significant inverse relationship between age and SpO_2 nadir.
Uong et al, 2001 [65]	Cross-sectional study	IV	11 children with Down syndrome and without OSAS (3.2 ± 1.4 y.o.); 14 control subjects (3.3 ± 1.1 y.o.)	Magnetic resonance imaging of the upper airway was performed. Subjects with Down syndrome had smaller airway volume than controls; $P < 0.005$). Subjects with Down syndrome had smaller mid- and lower face skeleton and shorter mental spine-clivus distance, hard palate length and mandible volume. Adenoid and tonsil volume was significantly smaller in the subjects with Down syndrome. Tongue, soft-palate, pterygoid, and parapharyngeal fat pads were of similar size to those of control children.
Marcus et al, 1991 [66]	Retrospective, cohort study	IV	53 children with Down syndrome (mean age 7.4 ± 1.2 [SE] years; range 2 weeks to 51 years)	A daytime nap polysomnogram was performed; 16 children also underwent nocturnal polysomnography. Nap polysomnograms were abnormal in 77% of children; 45% had OSAS, 4% had central apnea, and 6% had mixed apneas; 66% had hypoventilation (end-tidal PCO_2 >45 mm Hg) and 32% desaturation (SpO_2 <90%). Overnight studies were abnormal in 100% of children: 63% of children had OSAS, 81% had hypoventilation and 56% had desaturation. There was no clinical suspicion of OSAS in 36 (68%) children. Polysomnograms improved in 8 children who had adenotonsillectomy,

				but normalized in only 3. Patients with Down syndrome frequently have OSAS, hypoxemia, and hypoventilation.
Stebbens et al, 1991 [67]	Retrospective, cohort study	IV	32 children with Down syndrome (median age 1.4 years; range 0.1-4.9 years)	Parental questionnaires questionnaires were completed and chest wall movements and SpO_2 were recorded. Children with Down syndrome had increased frequency of stridor and chest wall retractions during sleep, reduced baseline SpO_2, increased frequency of $SpO_2 \leq 90\%$ in the presence of chest wall movements.
Ehlers-Danlos syndrome				
Guilleminault et al, 2013 [68]	Retrospective, cohort study	IV	34 patients with Ehlers-Danlos syndrome and symptoms of fatigue and poor sleep; 9 additional patients were followed prospectively	All participants underwent polysomnography. Apneas, hypopneas and flow limitation were detected. Frequency of flow limitation decreased with increasing age and apneas and hypopneas increased. Symptoms improved after implementation of nasal CPAP.
Mucopolysaccharidoses				
Mesolella et al, 2013 [69]	Retrospective, cohort study	IV	20 patients (7 female; median age 6 years at the beginning of the observation 6) with mucopolysaccharidosis (35% type I; 30% type II; 20% type III; 5% type IV; 10% type VI)	Recurrent otitis media was recorded in 30% of cases, hearing loss in 75%, adenotonsillar hypertrophy in 75%, frequent infections of the upper airway in 75% and OSAS in 45% of cases. 50% of participants underwent surgical therapy (adenotonsillectomy, adenoidectomy with insertion of middle ear ventilation tubes, tonsillectomy, tracheotomy and resection of vocal cord polyps).
John et al, 2011 [70]	Cross-sectional study	IV	28 children with mucopolysaccharidosis type VI (mean age 98.5 months)	Main symptoms and signs included: snoring, apnea, pectus carinatum, and macroglossia. 85.1% of subjects had OSAS; pulmonary hypertension was demonstrated in 14 patients by echocardiography and was associated with SpO_2 nadir.
Lin et al, 2010 [71]	Cross-sectional study	IV	24 patients with mucopolysaccharidosis (2 females; 3 with type I, 15 with type II, 1 with type III, 1 with type IV, and 4 with type VI; mean age, 10.8 ± 6 years; age range, 2.0-23.7 years)	Nadir SpO_2 was 74.5 ± 12.3%, and average % sleep time with SpO_2 <95% was 39.4%. Respiratory disturbance index was 21.8 ± 20.4 episodes/h, obstructive AHI was 21.4 ± 19.9 episodes/h, central apnea index was 0.4 ± 0.6 episodes/h and desaturation index was 17.6 ± 17.8 episodes/h. The

				prevalence of moderate to severe OSAS was 88%. Enzyme replacement therapy in 2 patients with mucopolysaccharidosis type II was accompanied by reduction in RDI (from 38.9-10.8 to 3.5-2.0 episodes/h).
Santamaria et al, 2007 [72]	Cross-sectional study	IV	5 children and 6 adults with mucopolysaccharidosis; healthy controls	Polysomnography and upper airway CT scan and endoscopy were performed. Retropalatal and retroglossal spaces were calculated through computed tomography, and the degree of adenoid hypertrophy was assessed through endoscopy. Apnea index and AHI were significantly higher in children than in adults with mucopolysaccharidoses. Retropalatal and retroglossal spaces were significantly smaller in patients compared to healthy controls. All subjects had adenoid hypertrophy causing upper obstruction on endoscopy.
Prader-Willi syndrome				
Cohen et al, 2014 [73]	Retrospective, cohort study	IV	44 patients with Prader-Willi (0.3-15.6 years old; 23 subjects <2 years of age)	Children <2 year old had more frequently central sleep apnea compared to older children (43% vs. 5%; P = 0.003). Obstructive events were prevalent in older children. Supplemental oxygen was used in 9 infants with Prader-Willi syndrome and central sleep apnea and the median central apnea index decreased from 14 to 1 episode/h (P = 0.008).
Sedky et al, 2014 [74]	Quantitative review	-	14 studies of children with Prader-Willi syndrome and who underwent polysomnography in order to exclude OSA (n = 224 children)	Prevalence of OSA across studies was 79.91% (179/224); 53.07% had mild OSA, 22.35% moderate OSA, and 24.58% severe OSA. Younger children and those with higher BMI z scores had higher AHI. Narcolepsy was present in 35.71% of cases. Adenotonsillectomy was associated with improvement in OSA for most children but residual OSA was present in the majority of cases postoperatively.
Vandeleur et al, 2013 [75]	Retrospective, cohort study	IV	34 children with Prader-Willi syndrome (age 3 months-16.3 years) who underwent polysomnography over a period of 8 years prior to initiation of treatment with growth hormone	15 of 34 children had OSAS (obstructive AHI > 1 episode/h). Patients with OSAS were significantly older (P = 0.009) and more likely to have hypertrophic tonsils (P = 0.05) compared to participants without OSAS. The two groups did not differ in BMI z-

				score or frequency of OSAS symptoms.

Question 1.3. Which techniques can be used for the objective evaluation of abnormalities predisposing to obstructive SDB?				
a. *Lateral neck X-ray*				
Author, year	**Type of Study**	**Class**	**Subjects**	**Methods and findings**
Xu et al., 2006 [76]	Retrospective, cohort study	IV	50 children (4-18 y.o.) with suspected OSAS	Participants had history collection, physical examination, lateral neck X-ray and nocturnal polysomnography on the night of clinical assessments. Thirty-one children had OSAS (AHI > 5 episodes/h, and 19 children had primary snoring (AHI ≤5 episodes/h). The combination of observed apnea, nocturnal enuresis, intrusive naps, mouth breathing, enlarged tonsils and radiologic features of narrowing had sensitivity 93.5%. specificity 42.2% positive predictive value of 72.5% and a negative predictive value of 80% for OSAS.
Jain et al., 2002 [77]	Prospective cohort study	IV	40 children (4-12 y.o.) undergoing adenoidectomy and/or tonsillectomy.	Children had pre- and post-operative polysomnography, clinical examination and lateral neck X-ray. All patients with a relative adenoid size greater than 0.64 were diagnosed with OSAS (AHI>5 episodes/h).
Li et al., 2002 [78]	Prospective cohort study	IV	35 children (median age 6.2 years) with suspected OSAS	Tonsillar size was evaluated by the tonsillar-pharyngeal ratio on the lateral X-ray and OSAS severity by polysomnography. Tonsillar–pharyngeal ratio >0.479 predicted AHI >10 episodes/h with sensitivity 95.8%, specificity 81.8%, positive and negative predictive values of 92% and 90%, respectively.
Brooks et al., 1998 [79]	Prospective study	III	33 children with suspected OSA	Lateral neck X-ray was performed and adenoid size was evaluated by the adenoidal-nasopharyngeal ratio. Tonsil size was assessed by physical examination. Mean respiratory disturbance index was 12.5 ± 9.1 episodes/h. Children with OSAS had a larger adenoid/nasopharyngeal ratio with reasonable positive and negative predictive values of 71% and 75% respectively.

b. *Flexible nasopharyngoscopy*				
Author, year	**Type of Study**	**Class**	**Subjects**	**Methods and findings**
Alonso-Alvarez et al, 2014 [23]	Cross-sectional, multicenter study	IV	248 obese children (BMI ≥ 95th percentile for age and sex; 54.4% males) with mean age 10.8 ± 2.6 years (range 3-14 years) and mean BMI 28.0 ± 4.7 kg/m^2 (96.8 ± 0.6 percentile) were randomly selected from primary care centers	The Pediatric Sleep Questionnaire (PSQ) was completed and nasopharyngoscopy and polysomnography were performed. Choanal obstruction by adenoidal hypertrophy was classified using nasopharyngoscopy: 75–100%, 50–75%, 25–50%, 0–25%. The mean respiratory disturbance index, obstructive respiratory disturbance index, and obstructive AHI were 5.58 ± 9.90 episodes/h, 5.06 ± 9.57 episodes/h, and 3.39 ± 8.78 episodes/h, respectively. The prevalence of OSAS ranged from 21.5% to 39.5% if obstructive AHI, obstructive respiratory disturbance index, or respiratory disturbance index ≥ 3 episodes/h were used as cut-off values.
Bravo et al, 2005 [80]	Cross-sectional study	IV	52 children with Pierre Robin sequence (median age 1 year and 7 months; range: 1 month-4 years old; 29 female).	A questionnaire regarding children's sleeping habits and sleep symptoms. Each child underwent a general pediatric examination, evaluation of craniofacial characteristics and upper airway patency, polysomnography and video nasopharyngoscopy. Video nasopharyngoscopy had 87% sensitivity and 100% specificity for the detection of OSAS. Video nasopharyngoscopy findings showed significant correlation with AHI, arousal index, snoring time, percentage of sleep time with SpO_2 <90%.
c. *i) Cephalometry; ii) MRI or CT of the upper airway; iii) functional respiratory imaging; iv) acoustic pharyngometry*				
Author, year	**Type of Study**	**Class**	**Subjects**	**Methods and findings**
i) Cephalometry				
Katyal et al., 2013 [34]	Systematic review and meta-analysis	-	9 studies were reviewed and 6 studies were included in the meta-analysis	ANB angle is the difference of angle between sella, nasion and A-point (SNA) and angle between sella, nasion and B-point (SNB). Children with OSA and primary snoring have increased weighted mean differences in the ANB angle of 1.64 degrees (P <0.0001) and 1.54 degrees (P <0.00001), respectively, compared to controls. Children with OSA have a reduced distance from the posterior nasal spine to the nearest adenoid tissue compared to controls. Thus, there is statistical evidence for craniofacial disharmony in children with SDB. However, differences from the

				controls are small and of uncertain clinical significance.
ii) MRI or CT of the upper airway				
Morimoto et al, 2014 [81]	Cross-sectional study	IV	35 patients with mucopolysaccharidosis and age 2-16 years (mean: age 9.2 ± 4.4 years); 45 control patients who underwent tracheal CT for other conditions.	The majority of patients had mucopolysaccharidosis type I (n=5) or type II (n=25). The cross-sectional area of the trachea was measured by CT. Airway obstruction was evaluated by endoscopy and was classified into Grades 0, 1, and 2. Tracheal morphology was abnormal in 50-60% (transversely collapsing narrow trachea). The tracheal cross-sectional area was smaller in patients with mucopolysaccharidosis compared to controls.
Cappabianca et al, 2013 [82]	Case-control study	III	40 children with OSAS and 40 controls	Besides the expected and previously described differences of minimum retropharyngeal cross-sectional area (CSA), nasopharyngeal airway, combined upper airway volume, tonsillar and adenoid cross-sectional and volumetric indices, a higher midsagittal CSA of the soft palate and lower position of the hyoid bone, SNB angle and mandibular volume were found. MRI facilitated the selection of appropriate surgical treatment.
Fricke et al, 2006 [83]	Cross-sectional study	III	52 subjects with persistent OSAS after adenotonsillectomy (9.71 ± 5.63 y.o.) and 37 control subjects (5.62 ± 3.77 y.o.)	Cine MRI studies for all subjects. Enlargement of the lingual tonsils was relatively common in children with persistent OSAS after adenotonsillectomy especially in patients with Down syndrome.
Rachmiel et al, 2005 [84]	Retrospective, cohort study	IV	12 patients (ages 12 months to 7 years) with mandibular deficiency and symptoms of OSAS who underwent mandibular distraction osteogenesis.	Patients had volumetric evaluation of the mandible and upper airway using three-dimensional-CT before and after the intervention. This study involved Three-dimensional CT demonstrated increase in mandibular volume by a mean of 28.24% and upper airway volume by a mean of 71.92%. Apnea and oxygen saturation improved and OSAS symptoms resolved.
Abbott et al, 2004 [85]	Cross-sectional study	IV	31 children with OSAS (mean age, 11.3 years) and 21 children free of airway symptoms (mean age, 3.5 years)	Transverse fast gradient-echo cine MR images of the hypopharynx were completed and volume segmentation was applied these images to quantify airway volumes at each time. Airway wall motion was also recorded. There were

				large fluctuations during respiration in children with OSAS and minimal fluctuations in controls. Average airway transverse volume was larger in the group with OSAS compared to the control group.
Arens et al, 2003 [86]	Cross-sectional study	III	20 children with OSAS and 20 control children (age 3.7 ± 1.4 years versus 3.9 ± 1.7 years, respectively).	Participants were studied by MRI of the upper airway with automatic segmentation. Mean and minimal cross-sectional area, length, and volume of: the total airway and of the regions along the adenoid, tonsils, and the adenoid and tonsils overlap were studied. Children with OSAS had significantly smaller mean cross-sectional area of the total airway compared to the control group, 28.1 ± 12.6 versus 47.1 ± 18.2 mm^2, respectively ($P < 0.0005$). Minimal cross-sectional area and airway volume were smaller in the OSAS group than in the control group: 4.6 ± 3.3 versus 15.7 ± 12.7 mm^2 ($P < 0.0005$) and 1.129 ± 515 versus 1.794 ± 846 mm^3 ($P < 0.005$), respectively. In children with OSAS the upper airway is most restricted where the adenoid and tonsils overlap.
Donnelly et al, 2003 [87]	Cross-sectional study	IV	16 young patients with OSA; 16 young patients with no airway symptoms of airway disease.	Cine magnetic resonance (MR) images were obtained while the subjects were asleep and showed significant differences in the patterns of dynamic airway motion between young patients with and without OSAS.
Fregosi et al, 2003 [88]	Cross-sectional study	IV	18 awake children (7-12 y. o.) with obstructive AHI ranging from 1.81 to 24.2 episodes/h.	Participants were classified into subjects with low obstructive AHI (2.8 ± 0.7 episodes/h; n = 9) or those with high obstructive AHI (13.5 ± 4.9 episodes/h; n = 9). MRI of the pharynx was performed. There was a significant positive correlation between obstructive AHI and tonsillar size ($r^2 = 0.42$; $P = 0.024$) or soft palate ($r^2 = 0.33$; $P = 0.049$). Obstructive AHI was inversely correlated with the volume of the oropharyx ($r^2 = 0.42$; $P = 0.038$). The narrowest point in the pharyngeal airway was smaller in the high-AHI group compared to the low-AHI group (4.4 ± 1.2 vs. 6.0 ± 1.3 mm; $P = 0.024$). In most subjects, the retropalatal airway was the narrowest point in the pharynx (overlap

				of soft palate, adenoid and tonsils).
Arens et al, 2001 [89]	Cross-sectional study	IV	18 children with OSAS (age 4.8 ± 2.1 year; 6 females; apnea index 4.3 ± 3.9 episodes/h) and 18 matched control subjects (age 4.9 ± 2.0 years; 6 females).	All participants underwent MRI under sedation. Axial and sagittal T1- and T2-weighted sequences were obtained and images were analyzed using image-processing software. Linear, area, and volumetric measurements of the upper airway and the tissues were carried out. The volume of the upper airway was smaller in subjects with OSAS as compared to control subjects (1.5 ± 0.8 versus 2.5 ± cm^3; $P < 0.005$) whereas the volume of the adenoid and tonsils were larger (9.9 ± 3.9 and 9.1 ± 2.9 cm^3 versus 6.4 ± 2.3 and 5.8 ± 2.2 cm^3, respectively; $P < 0.05$). Children with OSAS and controls did not differ in volumes of the mandible and tongue but the soft palate was larger in subjects with OSAS.
iii) Functional respiratory imaging				
Van Holsbeke et al, 2013 [90]	Cross-sectional study	IV	33 children with suspected OSA and mean age 6 ± 3.2 years (23 children with OSA on polysomnography)	A CT scan was completed during wakefulness, a three-dimensional reconstruction of the pharyngeal airway was prepared from these images, and computational fluid dynamics modeling of low inspiratory flow was performed. Children with OSA had significantly lower volume of the overlap region between tonsils and the adenoids, and lower mean cross-sectional area at this level. There was a significant correlation between upper airway conductance and AHI. No differences or significant correlations were observed with clinical parameters of upper airway patency. Functional imaging parameters are highly correlated with OSAS severity.
iv) Acoustic pharyngometry				
Monahan et al, 2002 [91]	Cross-sectional, community-based study	IV	203 children (8-11 y.o.)	Home cardiorespiratory monitoring was performed. Pharyngeal dimensions were evaluated by acoustic pharyngometry. Pharyngeal cross-sectional area was significantly reduced in preterm children, habitual snorers, and children with SDB compared to unaffected children. Thus, minimum cross-sectional area is a useful measure of risk factors for SDB.

Question 1.4. Which conditions from the past medical and family history are significant predictors of obstructive SDB?				
a. *Prematurity*				
Author, year	**Type of Study**	**Class**	**Subjects**	**Methods and findings**
Manuel et al, 2013 [92]	Cross-sectional study	IV	1,038 children with symptoms of SDB referred for airway evaluation and surgery. Fifty-seven of then had history of premature birth (mean age 62.09 ± 34.91 months; range, 4-190 months). The mean gestational age was 30.3 ± 4.0 weeks.	Children underwent nocturnal oximetry preoperatively. Multivariable analysis was used to identify factors predicting abnormal pulse oximetry. The prevalence rate of prematurity among patients treated surgically for SDB was 5.5% (95% CI 5.2-5.8). 23 (40%) and 17 (29.8%) subjects with history of prematurity had pulmonary and gastrointestinal comorbid disorders, respectively. The frequency of large airway abnormalities (mostly subglottic stenosis and laryngeal paralysis) was 19.3%. Comorbid respiratory disease was negatively associated with frequency of abnormal pulse oximetry (coefficient -0.35, $P<0.05$), whereas abnormal oximetry predicted postoperative respiratory outcomes.
Raynes-Greenow et al, 2012 [93]	Retrospective cohort study	III	Record linked population health data of 398,961 children, born between 2000 and 2004 (2.5-6 y.o.; New South Wales, Australia)	The primary outcome was a diagnosis of sleep apnea between 1 and 6 years of age (ICD-10 code G47.3: sleep apnea, central or obstructive). A total of 4,145 (1.0%) children (44.2 ± 13.9 m.o.) with a first diagnosis of sleep apnea were identified. History of adenoidectomy and/or tonsillectomy was present in 85.6% of children with sleep apnea. Children born preterm compared to term were significantly more likely to be diagnosed with sleep apnea (< 32 weeks versus term hazard ratio 2.74 [95% CI: 2.16, 3.49]) even after adjustment for confounding variables. Children born small for gestational age were not at increased risk of sleep apnea compared to children born appropriate for gestational age.
Sharma et al, 2011 [94]	Retrospective cohort study	IV	Records of 12 premature infants with bronchopulmonary dysplasia followed in a pediatric pulmonology clinic and diagnosed with OSAS were reviewed (mean gestational age 27 weeks; mean age at diagnosis 19 months).	AHI was 1-120 episodes/h and SpO_2 nadir was 50 -91%. After adenotonsillectomy, 6 children were re-evaluated all had persistent SDB.
Calhoun et al, 2010 [95]	Cross-sectional, population-based study	IV	613 school-aged children; 105 referred to the sleep clinic and 508 control	Children underwent polysomnography, history and physical examination. A

			subjects from the community	significant association was demonstrated between history of premature birth and moderate to severe SDB in childhood.
Montgomery-Downs et al, 2010 [96]	Cross-sectional study	IV	173 prematurely-born infants (9.13 months corrected age) followed at clinic	8.1% of infants (mean gestational age 31.6 weeks) were snoring ≥ 3 days/week. Birth weight and size for gestational age did not differ between groups with or without snoring. Infants with higher SDB symptom profiles had lower weight for age.
Hibbs et al, 2008 [97]	Prospective, population-based, cohort study	IV	383 children from the Cleveland Children's Sleep and Health Study who were born prematurely (<37 weeks gestational age) and who had sleep studies performed at ages 8 to 11 years (92% of all preterm children).	Twenty-eight children (7.3%) had SDB at age 8 to 11 years. Having a single mother and mild maternal preeclampsia were associated with SDB. Xanthine use and cardiopulmonary resuscitation or intubation in the delivery room were risk-factors for SDB in unadjusted analyses. Gestational age and birth weight were not significant risk factors for SDB at school age.
Paavonen et al, 2007 [98]	Retrospective cohort study	III	158 young adults born with very low birth weight and 169 term-born control subjects (18.5-27.1 y.o.).	SDB was defined as chronic snoring. The crude prevalence of SDB was similar in both groups: 15.8% for the very low birth weight group versus 13.6% for the control group. However, SDB was 2.2 times more likely in the very low birth weight group compared with the control group after adjustment for other confounding factors.
Rosen et al, 2003 [99]	Population-based cohort study	I	850 children (41% black, 46% preterm), aged 8-11 years.	Children underwent overnight in-home cardiorespiratory recordings of airflow, respiratory effort, oximetry, and electrocardiography. Using the most inclusive definition, SDB was detected in 40 (4.7%) children. Depending on the definition used, SDB was 3-5 times more likely in former preterm compared with term children.
b. *Family history of SDB*				
Author, year	**Type of Study**	**Class**	**Subjects**	**Methods and findings**
Alexopoulos et al, 2014 [100]	Retrospective, cohort study	III	Data of 798 children (median age 5.8 years; range 2-15 years) without history of prior AT, neuromuscular, or genetic disorders or craniofacial abnormalities who were referred for polysomnography were analyzed.	69.3% of children had tonsillar hypertrophy, 25.8% were obese, 26.8% had at least one parent with history of adenoidectomy and/or tonsillectomy, and 22.1% had AHI >5 episodes/hour. Parental history of adenoidectomy and/or tonsillectomy was significantly associated with moderate-to-severe OSAS (logit model including gender,

				tonsillar hypertrophy, obesity, and physician-diagnosed wheezing; OR [95% CI], 1.70 [1.18-2.46]; P < .01). Tonsillar hypertrophy combined with history of adenoidectomy and/or tonsillectomy in at least one of the parents had high specificity (84.4%) and the highest positive likelihood ratio (1.78) for identifying children with AHI >5 episodes/hour.
Kalampouka et al, 2014 [101]	Cross-sectional study	IV	Two hundred ninety-two children (2-14 y.o.) recruited from the emergency department or the pediatric pulmonology clinic	37 (12.7%) of them had paternal history of adenoidectomy and/or tonsillectomy, 39 (13.4%) maternal history of adenoidectomy and/or tonsillectomy, 60 (20.5%) tonsillar hypertrophy, and 48 (16.4%) history of habitual snoring. Maternal and paternal history of adenoidectomy and/or tonsillectomy were significantly associated with presence of tonsillar hypertrophy after adjustment for age, gender, obesity, passive smoking, and physician-diagnosed wheezing requiring treatment with inhaled medications over the past year [odds ratios (95% confidence interval): 3.52 (1.54-8.06); P < 0.01 and 4.70 (2.13-10.36); P < 0.01, respectively]. Only maternal history of adenoidectomy and/or tonsillectomy predicted history of snoring [4.12 (1.86-9.12); P < 0.01].
Lundkvist K, 2012 [102]	Retrospective, cohort study (hospital records)	III	Data of 3 million children (0-18 y.o.) in Sweden over a period of 11 years were analyzed to identify admissions for the first time to hospitals for OSAS, adenotonsillar or tonsillar hypertrophy.	Children were categorized in two groups: having or not having a parent with OSAS diagnosis. After adjustment for socio-economic status, age, and geographic region, the standardized incidence ratios of OSAS in boys and girls with parental history of OSAS compared to those without such a history were: 3.09 (95% CI 1.83-4.90) and 4.46 (95% CI 2.68-6.98), respectively. The standardized incidence ratios of adenotonsillar or tonsillar hypertrophy in boys and girls with parental history of OSAS compared to those without were: 1.82 (95% CI 1.54-2.14) and 1.56 (95% CI 1.30-1.87), respectively.
Friberg et al, 2009 [103]	Retrospective, cohort study	IV	Data of 2.7 million individual < 19 years old who were born between 1978 and	The population of Sweden aged 0-18 years and born between 1978 and 1986

			1986 were analyzed to determine the initial hospital admission for OSAS, adenotonsillar hypertrophy or tonsillar hypertrophy during the follow-up period 1997-2004.	was divided into sibling groups based on a shared mother and father. and presence of a primary hospital diagnosis of OSAS or adenotonsillar hypertrophy for each individual born between 1978 and 1986. After adjustment for socioeconomic status, age, and geographic region, boys with at least one sibling with OSAS had an increased risk of having OSAS compared to those without such a history (standardized incidence ratio, 33.2; 95% CI, 16.5-64.8), and in girls 40.5 (19.4-81.4). For hypertrophy of the tonsils or adenotonsillar hypertrophy the corresponding standardized incidence ratios were 4.53 (3.0-6.8) for boys and 4.94 (3.3-7.4) for girls.
Ovchinsky et al, 2002 [104]	Case-control study	IV	497 of 600 children who had nap polysomnograms over a 6-year period were positive for OSAS. A caretaker of 200 of the 497 children with OSAS was contacted, and 115 were recruited in the study.	SDB in first-degree relatives was assessed by questionnaire-type telephone interviews with the current caretakers. Data were collected for 445 first-degree relatives (256 adults and 189 children) of the 115 children who had a nap study positive for OSAS. Habitual snoring was reported in 194 (43.6%) of the family members. 68 (26.6%) of the adult first-degree relatives and 23 (12.2%) of the pediatric first-degree relatives had symptoms suggestive of OSAS. Of the 115 children with positive nap study, 50 (43.5%) had at least 1 relative with symptoms consistent with OSAS; 6 (1.3%) of the first-degree relatives had polysomnography results positive for OSAS, 4 (0.9%) were using nasal continuous positive airway pressure, and 21 (4.7%) had underwent surgery for OSAS.
Redline et al, 1999 [31]	Population-based study	III	399 children (2-18 y.o.) members of families with a member (a proband) with diagnosed OSAS or as members of neighborhood control families.	All children underwent overnight multichannel monitoring (airflow, chest wall impedance, pulse oximetry and heart rate) at home and SDB was defined as AHI $\geq$ 10 episodes/h. Absence of SDB was defined as AHI <5 episodes/h. SDB was diagnosed in 1.6% of children from control families and in 8.4% of children from families with family history of OSAS (P=0.009).

Online Supplementary Table 2.

Step 2: Recognition of morbidity and conditions frequently co-existing with SDB

Question 2.1. Which abnormalities have increased prevalence in children and adolescents with obstructive SDB and reflect associated morbidity?				
Morbidity from the cardiovascular system				
a. *Elevated blood pressure and heart rate*				
Author, year	**Type of Study**	**Class**	**Subjects**	**Methods and findings**
Hannon et al, 2014 [105]	Case-control study	IV	Overnight polysomnography and morning blood pressure measurements were performed in obese (BMI >95th percentile) non-diabetic adolescents (12-18 y.o.; n = 49) who were divided into two subgroups: with normal blood pressure or with elevated blood pressure.	Adolescents without and those with elevated blood pressure did not differ in terms of AHI (2.9 ± 2.9; 0.1-12.4 episodes/h vs. 4.6 ± 5.5; 0.0-20 episodes/h, respectively; P=0.88)
Quante et al, 2014 [106]	Multicentre, single-blind, randomised, controlled trial	I	464 children (5-9 y.o.) with OSAS randomly assigned to early adenotonsillectomy (median baseline obstructive AHI 4.8 episodes/h) or watchful waiting (median baseline obstructive AHI 4.5 episodes/h). OSAS was defined as an obstructive AHI ≥2 episodes/h or an obstructive apnea index ≥1 episode/h.	There was a positive association between nocturnal heart rate and baseline OSAS severity (average heart rate increase of 3 beats per minute for AHI of 2 versus 10 episodes/h. For each 5-unit improvement in AHI and 5 mmHg improvement in peak end-tidal CO2 there was a reduction in heart rate by 1 and 1.5 beats per minute, respectively.
Xu et al, 2013 [107]	Cross-sectional study	IV	145 children with snoring were recruited	Polysomnography and ambulatory blood pressure monitoring was carried out. OSAS was defined as AHI >5 episodes/h or obstructive apnea index >1 episode/h. Blood load, blood pressure index and nocturnal blood pressure dipping were calculated for each child. 107 children were found to have OSAS. Children with and without OSAS did not differ in terms of age or gender distribution. Children with OSAS had higher mean nocturnal systolic and diastolic blood pressure, increased blood pressure load, and decreased nocturnal blood pressure dipping than children without OSAS (systolic blood pressure: P = 0.03; diastolic blood pressure: P < 0.001; blood pressure load: P = 0.001; systolic blood pressure dipping: P = 0.03; diastolic blood pressure dipping: P = 0.04). Multivariable analysis revealed that mean nocturnal systolic blood pressure was associated significantly with age, obesity, and oxygen desaturation index

				(P = 0.04, 0.03, and 0.02 respectively). Mean nocturnal diastolic blood pressure was related to obesity and oxygen desaturation index (P = 0.03 and 0.04, respectively).
Horne et al, 2011 [108]	Cross-sectional study	IV	105 children referred for suspected OSAS and 36 control children without snoring (7-13 y.o.)	Children underwent polysomnography and continuous blood pressure monitoring. Blood pressure while awake before sleep onset and during nocturnal sleep was elevated by 10 to 15 mm Hg in the SDB group compared to the control group independent of SDB severity. Blood pressure during stable sleep (respiratory events and movements excluded) was elevated in participants with OSAS compared to the control group.
Amin et al, 2008 [109]	Cross-sectional study	IV	140 participants: i) children (7-13 y.o.) with adenotonsillar hypertrophy, nightly snoring and AHI ≥1 episode/h; ii) age- and gender-matched healthy controls	24-hour ambulatory blood pressure monitoring revealed that children with obstructive AHI >5 episodes/h have an approximate mean increase of 3.5 mmHg in average wake systolic and wake and sleep diastolic blood pressure compared to healthy controls without snoring and with AHI ≤1 episode/h. Wake and sleep systolic, diastolic and mean blood pressure are significant predictors of changes in the relative wall thickness of the left ventricle.
Li et al, 2008 [110]	Cross-sectional, community-based study	IV	306 children (6-13 y.o.)	Nocturnal sleep study and ambulatory blood pressure monitoring was performed. 306 children with OSAS (obstructive AHI ≥1 episode/h) and controls (snoring <3 nights/week and AHI <1 episode/h). Children with moderate-to-severe OSAS (AHI >5 episodes/h) had significantly higher blood pressure than subjects with mild OSAS (1-5 episodes/h) or controls while awake or asleep. Children with moderate to severe OSAS (AHI >5) were at significantly higher risk for nocturnal systolic (OR 3.9 (95% CI 1.4 to 10.5)) and diastolic (OR 3.3 (95% CI 1.4 to 8.1)) hypertension (blood pressure over the 95th percentile for age, gender and height) compared to controls.
Li et al, 2009 [111]	Cross-sectional, community-based study	IV	190 children (6-13 y.o.); 56 nonsnoring controls, 46 children with primary	Nocturnal sleep study and ambulatory blood pressure monitoring. Nocturnal

			snoring, 62 children with AHI 1-3 episodes/h, and 26 children with an AHI > 3 episodes/h	diastolic blood pressure was significantly higher in children with primary snoring compared to controls after adjustment for age, gender, and body mass index.
Zintzaras & Kaditis, 2007 [112]	Meta-analysis	-	5 pediatric cohort studies (published before July 2006) that investigated the relationship between SDB and blood pressure were analyzed.	There was no evidence that moderate to severe SDB in children increases the risk of elevated blood pressure. There was heterogeneity among the published studies.
b. *Pulmonary hypertension and cor pulmonale*				
Author, year	**Type of Study**	**Class**	**Subjects**	**Methods and findings**
John et al, 2011 [70]	Cross-sectional study	IV	28 children with mucopolysaccharidosis type VI (mean age 98.5 months)	Main symptoms and signs included: snoring, apnea, pectus carinatum, and macroglossia. 85.1% of subjects had OSAS; pulmonary hypertension was demonstrated in 14 patients by echocardiography and was associated with SpO_2 nadir.
Miman et al, 2000 [113]	Retrospective, cohort study	IV	17 children (20-96 months old) with adenotonsillar hypertrophy, SDB and pulmonary hypertension	Pulmonary arterial pressure was measured by Doppler echocardiography. Following adenoidectomy and/or tonsillectomy mean preoperative pulmonary arterial pressure decreased from 29.12 ± 4.41 mmHg to 12.06 ± 3.09 mmHg ($P<0.01$). Upper respiratory obstruction symptom score also decreased significantly postoperatively ($P<0.01$) in the postoperative period.
Lefaivre et al, 1997 [114]	Prospective, cohort study	IV	7 children with Down syndrome and OSAS (2 girls; 3-12 years old)	Surgical treatment for OSAS included tongue reduction (n = 6), tongue-hyoid advancement (n = 4), uvulopalatopharyngoplasty (n = 7), and maxillary or midface advancement (n = 2); 1 child was intubated preoperatively for respiratory failure, he was later found to have pulmonary hypertension and ultimately underwent tracheostomy. Patients had preoperative and postoperative nocturnal polysomnography and radiologic evaluation to assess the efficacy of surgical treatment in OSAS.
Jacobs et al, 1996 [115]	Retrospective, cohort study	IV	71 pediatric patients with Down syndrome and upper airway obstruction over a 5-year period	34 children had pulmonary arterial hypertension; 44 of 71 patients had multiple sites of airway obstruction. Abnormalities causing airway obstruction included included lymphoid hyperplasia, macroglossia, narrow

				nasopharynx, laryngomalacia, congenital subglottic stenosis, tracheobronchomalacia, and tracheal stenosis. Children with upper airway obstruction underwent surgical procedures including tonsillectomy, adenoidectomy, tonsillar pillar plication, uvulopalatopharyngoplasty, anterior tongue reduction, tongue-hyoid suspension, laryngotracheoplasty, and tracheotomy. 27 patients had mild obstructive symptoms, and most of them improved after tonsil or adenoid surgery, or both. The remaining patients were of younger age and had more severe symptoms, multiple sites of obstruction, and high incidence of cardiac disease. 11 (39%) of the 28 patients in this group had significant residual symptoms after surgery. Four children are tracheotomy-dependent. 5 deaths occurred and 3 of them were attributed to upper airway obstruction.
Melacini et al, 1996 [116]	Cross-sectional study	IV	21 wheelchair-bound patients with Duchenne muscular dystrophy (10-24 years old)	Patients underwent electrocardiogram and echocardiogram, spirometry, daytime arterial blood gas analysis, and nocturnal SpO_2 monitoring. Patients were classified into: group A normoxemic (14 subjects) and group B with nocturnal hypoxemia (7 cases). Group A was divided into 2 subgroups, one without (n=9; ejection fraction 56%), and one with left ventricular dilation (n=5; ejection fraction 32%). Analysis of pulsed Doppler pulmonary data indicated significant reduction in corrected time to peak velocity in group B patients, when compared with controls, A1, and A2 groups respectively. In group A, there was a correlation between ejection fraction and corrected time-to-peak velocity. Two patterns of cardiac involvement may be recognized in advanced-stage Duchenne muscular dystrophy: left ventricular wall motion abnormalities and dilated cardiomyopathy. Doppler data probably suggesting pulmonary hypertension may be observed in patients with dilated cardiomyopathy, and in patients with nocturnal hypoxemia.

Brown et al, 1988 [117]	Retrospective, cohort study	IV	11 children with adenotonsillar hypertrophy and cor pulmonale	Severity of disease ranged from mild (only abnormal ECG or chest X-ray) to severe (hypercarbia, hypoxia, and right heart failure); 1 patient with severe disease had respiratory arrest postoperatively; 4 patients with severe cor pulmonale were intubated and underwent assisted ventilation, postoperatively. Patients with cor pulmonale should be monitored in the Intensive Care Unit after adenotonsillectomy.
Morbidity from the central nervous system				
a. *Excessive daytime sleepiness*				
Author, year	**Type of Study**	**Class**	**Subjects**	**Methods and findings**
Khalyfa et al, 2011 [118]	Prospective cohort study	IV	80 children with OSAS (7.2 ± 0.2 y.o.), 80 age-, sex- and ethnicity-matched control children (7.2 ± 0.3 y.o.)	Morning TNF-a levels and Epworth Sleepiness Scale (ESS) scores were increased in children with OSAS. Among children with OSAS, TNF-a levels were markedly higher in the presence of -308G gene polymorphism (P<0.001). ESS scores were markedly increased in children with the TNF-a -308G polymorphism, but they were within the range measured in control children when this specific polymorphism was absent (P<0.001).
Tsaoussoglou et al, 2010 [119]	Case-control study	IV	150 children (9.26 ± 0.23 y.o.): overweight/obese with moderate SDB (n=17); overweight/obese with mild SDB (n=15); overweight/obese without SDB (n=42); lean control children (n=76)	Excessive daytime sleepiness frequency increased progressively and significantly in the four groups, with the lowest frequency in the lean control group (20%) and highest in the overweight/ obese moderate SDB group (70%) (P=0.001). Excessive daytime sleepiness was significantly more frequent in the overweight/ obese moderate SDB group compared with overweight/ obese without SDB group (P= 0.03).
Gozal & Kheirandish-Gozal, 2009 [120]	Prospective cohort study	III	50 obese children and 50 nonobese children (6-9 y.o.)	Multiple sleep latency for obese children was significantly reduced compared with that for nonobese children (P < 0.001). Significant linear correlations with the obstructive AHI, respiratory arousal index, and proportion of total sleep time spent with SpO_2 < 95% were noted. For all children, there was a significant association between BMI and multiple

				sleep latency (r=0.44; P=0.001)
Perez-Chada et al, 2007 [121]	Population-based, cross-sectional survey	IV	2884 students (mean age: 13.3 ± 1.5 years)	A Spanish version of the Pediatric Daytime Sleepiness Scale (PDSS) questionnaire was administered. Parental reporting of snoring occurred in 511 subjects (23%); snoring was occasional in 14% and frequent in 9%. Frequent snorers had higher mean PDSS scores than occasional or nonsnorers (18 ± 5, 15.7 ± 6 and 15.5 ± 6, respectively; P < 0.001).
Chervin et al, 2006 [122]	Prospective cohort study	I	103 children (5-12 y.o.)	Polysomnography followed by Multiple Sleep Latency Tests were performed. The Pediatric Sleep Questionnaire-Sleepiness Subscale (PSQ-SS) correlated inversely but not strongly with the mean sleep latency on the multiple sleep latency test (r=−0.23, p=0.006). Among children with sleep apnea, subjective sleepiness as an outcome in simple logistic regression models was predicted by the normalized apnea/ hypopnea index: OR = 2.6 (1.0-6.8).
Johnson & Roth 2006 [123]	Community-based survey	IV	1014 adolescents (13-16 y.o.)	Separate structured face to face diagnostic interviews of adolescents and parents were conducted. SDB was defined as report of loud snoring, gasping/choking or snorting, awakening with gasping or choking, or momentary periods of stopped or abnormal breathing occurring weekly. SDB was independently associated with excessive daytime sleepiness, poorer grades, and attention-deficit/hyperactivity disorder-inattention features.
Melendres et al, 2004 [124]	Prospective cohort study	IV	108 patients with suspected SDB (7 ± 4 y.o.) and 72 control subjects (8 ± 4 y.o.)	Polysomnography was performed in patients with suspected SDB. Patients with suspected SDB had higher modified Epworth Sleepiness Scale (ESS) (8.1 ± 4.9 vs 5.3 ± 3.9) and higher Conners Abbreviated Symptom Questionnaire score (12.8 ± 7.6 vs 9.0 ± 6.2) than control subjects. There was no difference in the ESS and Conners scores of patients with primary snoring and patients with OSAS. The ESS had weak correlations with polysomnographic parameters.
Urschitz et al, 2004 [125]	Population-based, cross-sectional	IV	1144 parents and their children (mean	Habitual snoring (snoring frequently or

	survey		age 9.6 ± 0.7 years) agreed to participate and returned a completed questionnaire.	always) and impaired behavior were assessed using parental questionnaires. Habitual snoring was significantly associated with daytime sleepiness.
Goodwin et al, 2003 [28]	Prospective, population-based, cohort study	IV	239 children from the community (6-11 y.o.)	Home unattended polysomnography. Excessive daytime sleepiness was diagnosed if parents reported that their child had any of the following frequently or almost always: child was sleepy in the daytime, fell asleep while watching TV or in school, or had problems falling asleep during the day. Subjects with respiratory disturbance index (RDI) ≥ 5 episodes/h (no desaturation necessary to define respiratory events) had higher prevalence of frequent snoring (20.3% vs 9.1%; P<0.01), excessive daytime sleepiness (22.9% vs 10.7%; P<0.01), and learning problems (8.5% vs 2.5%; P<0.04) compared to those with RDI < 5 episodes/h. RDI ≥ 1 episode/h (3% oxygen desaturation required for definition of respiratory events) was associated with higher prevalence of frequent snoring (24.0% vs 10.4%; P<0.006), excessive daytime sleepiness (24.0% vs 13.4%; P<0.04), and learning problems (10.7% vs 3.0%; P<0.02) than RDI < 1 episode/h.
Goodwin et al, 2003 [126]	Population-based, cross-sectional study	IV	1494 children (4-11 y.o.)	A 13-question sleep habits screening questionnaire designed to assess the severity of sleep-related symptoms associated with SDB was administered. Snoring was present if parents reported their child snored loudly "frequently" or "almost always". Excessive daytime sleepiness was significantly associated with snoring (adjusted OR= 3.2; 95% CI 1.8-5.5; p < 0.001).
Gottlieb et al, 2003 [127]	Population-based, cross-sectional survey	IV	3019 children (5 y.o.)	A parent-completed questionnaire was used to identify snoring and other SDB symptoms and the presence of daytime sleepiness and problem behaviors. SDB was defined as frequent or loud snoring; trouble breathing or loud, noisy breathing during sleep; or witnessed sleep apnea. Children with SDB symptoms were significantly more likely to have parent-

				reported daytime sleepiness (OR= 2.2; 95% CI 1.7 – 2.8) and hyperactivity (OR=2.5; 95% CI 2.0-3.0), inattention (OR=2.1; 95% CI 1.7-2.6), and aggressiveness (OR=2.1; 95% CI 1.6-2.6).
Shin et al, 2003 [128]	Population-based cross-sectional survey	IV	A total of 3,871 high school students (15-18 y.o.)	Prevalence of habitual snoring was 11.2%. Frequency of snoring increased significantly with BMI (P <0.001), cigarette smoking (P <0.01), prevalence of witnessed apnea (P <0.001), and Epworth sleepiness scale score (P <0.001).
Gozal et al, 2001 [129]	Prospective cohort study	I	54 children with OSAS, 14 children with primary snoring, and 24 controls	Participants underwent an overnight diagnostic polysomnogram followed the next day by a multiple sleep latency test. Mean apnea index (±SD) was 15.1 ± 9.5 episodes/h in OSAS, 1.1 ± 0.5 episodes/h in primary snoring, and 0.1 ± 0.3 episodes/h in controls. Mean sleep latencies were: 23.7 ± 3.0 minutes in controls, 23.7 ± 3.1 minutes in primary snoring, and 20.0 ± 7.1 minutes in OSAS patients. However, only 7 children with OSAS had mean sleep latencies <10 minutes. Sleep latencies were more likely to be shorter in OSAS patients with more severe apnea index (r= -075; P < 0.0001), higher arousal index (r= -0.69; P<0.001), higher percent of total sleep time spent with SpO_2 below 90% (r= -0.70; P < 0.001) and higher BMI (r= -0.78; P < 0.0001). Thus, shortened sleep latencies occur in children with OSAS, but excessive daytime sleepiness is infrequent and tends to develop among more severe and/or obese patients.
b. *Inattention/hyperactivity*				
Author, year	**Type of Study**	**Class**	**No. of subjects**	**Methods and findings**
Perfect et al, 2013 [130]	Prospective, population-based cohort	I	263 children evaluated in preadolescnce and approximately 5 years later in adolescence	Polysomnography and neurobehavioral assessment were performed at two time points approximately 5 years apart. Behavior assessment scale for children-2(nd) Edition parent report form (BASC-PRF) and Self-Report of Personality (SRP), and the Adaptive Behavior Assessment System-2(nd) Edition (ABAS-2) were used. Compared to those who never had SDB, individuals with persistent SDB had significant odds and

				met more cutoff scores on the BASC-2-PRF externalizing problems composite (OR 3.29; 8.92% vs. 35.3%), behavioral symptoms index (OR 6.82; 7.4% vs. 35.3%) and hyperactivity subscale (OR 6.82; 11.1% vs. 41.2%). Greater difficulties were demonstrated for the group with persistent SDB (relative to never) on the ABAS-2 social domain (OR 3.39; 22% vs. 50%), and Communication (OR 4.26; 15% vs. 42.9%) and Self-Care subscales (OR = 2.97; 25.2% vs. 50%). Relative to subjects who never had SDB, subjects who developed SDB over the 5-year observation period had compromised adaptive skills as indicated by the BASC-2 PRF adaptive behavior composite (OR 3.34; 15.6% vs. 38.1%) and the ABAS-2 general adaptive composite (OR 2.83; 20.5% vs. 42.1%).
Sedky et al, 2014 [131]	Meta-analysis	-	*Relationship between SDB and attention-deficit, hyperactivity disorder symptomatology:* 18 studies with 1113 children in the clinical group (874 had SDB and were examined for attention-deficit, hyperactivity disorder symptoms; 239 had attention-deficit, hyperactivity disorder and were examined for SDB) and 1405 in the control-group. *Difference between attention-deficit, hyperactivity disorder symptomatology pre- versus post-adenotonsillectomy:* 12 studies (529 subjects) were identified assessing pre- versus post-surgery attention-deficit hyperactivity disorder symptoms	*Relationship between SDB and attention-deficit, hyperacivity disorder symptomatology:* Medium relationship was demonstrated between attention-deficit, hyperactivity disorder symptoms and SDB (Hedges' g=0.57, 95% CI 0.36-0.78; p< 0.001). A high AHI cutoff was associated with lower effect sizes, while child age, gender and BMI did not moderate the relationship between SDB and attention-deficit, hyperactivity disorder. Study quality was associated with larger effect sizes. *Difference between ADHD symptomatology pre- versus post-AT:* Hedges' g=0.43 (95% CI 0.30-0.55; p < 0.001) suggesting a medium effect i.e. adenotonsillectomy (for AHI ≥1 episode/h) was associated with decreased ADHD symptoms at 2-13 months postoperatively.
Cortese et al, 2009 [132]	Meta-analysis	-	Sixteen studies with a total pooled sample of 722 children with ADHD versus 638 controls.	*Subjective items:* children with attention-deficit, hyperactivity disorder had significantly higher bedtime resistance (z = 6.94; P <0.001), more sleep onset difficulties (z = 9.38; P <0.001), night awakenings (z = 2.15; P =0.031), difficulties with

				morning awakenings (z = 5.19; P <0.001), SDB (z = 2.05; P =0.040), and daytime sleepiness (z = 1.96; P =0.050) compared with the controls. *Objective parameters:* sleep onset latency (on actigraphy), the number of stage shifts/hour sleep, and AHI were significantly higher in children with attention-deficit, hyperactivity disorder compared with controls (z = 3.44; P =0.001; z = 2.43; P =0.015; z = 3.47; P =0.001, respectively). Children with attention-deficit, hyperactivity disorder also had significantly lower sleep efficiency on polysomnography (z = 2.26; P =0.024), true sleep time on actigraphy (z = 2.85; P =0.004), and average times to fall asleep for the multiple sleep latency test (z = 6.37; P <0.001) than controls.
Sadeh et al, 2006 [133]	Meta-analysis	-	11 journal articles, including 333 children with attention-deficit, hyperactivity disorder and 231 control children.	Measures related to sleep architecture, breathing disorders, and periodic limb movements in sleep (PLMS), and the role of potential moderators such as age, gender were analyzed. Sleep latency was longer in children with ADHD relative to controls in samples where children with comorbid conditions were excluded (d=0.37; P<0.05; 95% CI 0.11- 0.62). Children with ADHD are more likely than controls to suffer from PLMS. Factors such as age, gender, inclusion of adaptation night, and comorbidity play a moderating role in the associations between sleep characteristics and ADHD.
c. *Cognitive deficits and academic difficulties*				
Author, year	**Type of Study**	**Class**	**Subjects**	**Methods and findings**
Brockmann et al, 2012 [134]	Cross-sectional, community-based study	IV	1114 primary school children were used to identify children who never snored (N = 410) or snored habitually (N = 114).	Habitual snoring was diagnosed if parents responded that it was "frequently" or "always" present. Nocturnal home sleep study was performed in 92 habitual snorers using a portable device. AHI was the number of obstructive and mixed apneas and hypopneas per hour of corrected estimated sleep time. Respiratory disturbance index (RDI) was the number of

				obstructive and mixed apneas, hypopneas, and flow limitations per hour of corrected estimated sleep time. OSAS was defined as AHI ≥1 episode/h; upper airway resistance syndrome (UARS) was AHI <1 and RDI ≥1 episode/h, and primary snoring (PS) was AHI and RDI <1 episode/h with oxygen desaturation index <4 episodes/h. 69 habitual snorers had PS, 11 had UARS and 12 had OSAS. Compared to never snoring, PS was a significant risk factor (OR; 95% CI) for hyperactive behavior (2.8; 1.6-4.8), inattentive behavior (4.4; 2.4-8.1), and daytime sleepiness (10.7; 4.0-28.4). PS was also an independent risk factor for poor school performance in mathematics (2.6; 1.2-5.8), science (3.3; 1.2-8.8), and spelling (2.5; 1.1-5.5).
Biggs et al, 2011 [135]	Cross-sectional study	III	127 children (7-12 y.o.)	Subjects were classified into four groups by polysomnography: control (N=34); primary snoring (N=55), mild OSAS (N=22) and moderate to severe OSAS (N=16). The Behaviour Rating Inventory of Executive Function (BRIEF) was applied as parent-reported measure of working memory and revealed working memory deficits at all severities of SDB relative to controls. A computerised test involving immediate recognition of playing cards (CogHealth) was the objective measure of working memory and revealed significant differences only between mild OSA and primary snoring. Observation of deficits in working memory may be largely dependent on the assessment method.
Bourke et al, 2011 [136]	Cross-sectional study	IV	137 children (7-12 y.o.)	Subjects were classified into four groups by polysomnography: control (N=35); primary snoring (N=59), mild OSAS (N=24) and moderate to severe OSAS (N=19). Cognition and academic skills were evaluated using the Wechsler Abbreviated Scale of Intelligence (WASI), the Wide Range Achievement Test-3rd Edition (WRAT-3), the Rey Complex Figure Test (RCFT) and the Controlled Oral Word Association Test (COWAT).

				General intellectual ability: the full scale IQ scores of all three SDB groups were lower than the control group ($p < 0.001$). The verbal IQ scores of all three SDB groups were also lower than the control group ($p < 0.001$). *Academic ability:* No differences in mean scores for Reading, Spelling and Arithmetic between SDB groups and controls were found after adjustment for socio-economic status. *Executive skills:* No significant group differences were found for mean COWAT or RCFT z-scores. No significant relationship was identified between neurobehavioral outcome measures and respiratory parameters.
Miano et al, 2011 [137]	Prospective, cohort study	III	60 control subjects; 13 children with primary snoring; 31 subjects with OSA	Participants underwent the neurocognitive assessment. IQ estimates of controls were higher and the ADHD rating scale scores lower than those of children with SDB. In children with SDB, the percentage of wakefulness after sleep onset, of N1, of A2, of arousal and A2 index correlated positively with global intelligence. Total and hyperactivity scores correlated positively with the A2 index. A negative correlation was demonstrated between the hyperactivity score and nocturnal oxygen saturation.
Beebe et al, 2010 [138]	Cross-sectional study	IV	163 overweight subjects aged 10-16.9 years	Moderate-severe OSAS (AHI > 5 episodes/h): n = 42); mild OSAS (AHI = 1-5 episodes/h): n = 58; snorers (AHI <1 episode/h and snoring): n=26); non-SDB (AHI <1 episode/h and nonsnoring): n=37. The 4 groups differed significantly in academic grades and parent- and teacher-reported behaviors, particularly inattention and learning problems. Parent- and self-reported grades were associated with parent and teacher-reported attention problems (r= -0.47 to -0.57; $P < 0.001$). Teacher-reported learning problems (r = -0.51 to -0.53; $P < 0.001$) were found to be associated with SDB.
Calhoun et al, 2009 [139]	Prospective, community-based cohort	I	571 school-aged children (6-12 years)	9-hour nocturnal polysomnography and

	study			comprehensive neuropsychological battery (intelligence, verbal and nonverbal reasoning ability, attention, executive functioning, memory, processing speed, and visual-motor skill). Moderate SDB: n=6; mild SDB: n=152; non-SDB: n=413. No significant difference between the 4 study groups regarding any neurobehavioral measures except for the non-verbal IQ. No significant correlations between any neuropsychological measures and AHI.
Honaker et al, 2009 [140]	Prospective, population-based cohort	I	228 children (5-7 y.o.)	Nocturnal polysomnography and language assessment by DAS, NEPSY, EVT and PPVT-III. 76 children with OSA, 76 with primary snoring and 76 controls. Children of preschool age with SDB had difficulties in processing information with increasing linguistic complexity. School-aged children with SDB had reduced vocabulary knowledge or ability.
Kohler et al, 2009 [141]	Prospective cohort study	II	44 healthy snoring children (3-12 y.o.) scheduled for adenotonsillectomy; 48 age and gender matched non-snoring controls from the community	Participants underwent polysomnography and neurocognitive assessment at baseline and at 6 months (after surgery in the SDB group). Neurocognitive deficits were found at baseline in SDB children compared to controls including a 10-point IQ difference ($P<0.001$) and similar deficits in language and executive function. Adenotonsillectomy was accompanied by improved respiratory parameters at 6 months following surgery but neurocognitive performance did not change relative to controls.
Giordani et al, 2008 [142]	Case-control study	IV	27 healthy control children; 40 children with OSA and 27 children without OSA scheduled for adenotonsillectomy	Behavior, sleep problems, and snoring were rated by parents; specific cognitive measures regarding short-term attention, visuospatial problem solving, memory and arithmetic. Children undergoing adenotonsillectomy had overall greater difficulties compared to controls. Differences from controls were more apparent for children without OSAS undergoing adenotonsillectomy.
Hamasaki Uema et al, 2007 [143]	Retrospective cohort study	IV	81 children (6-12 y.o.): OSA, n=24; primary snoring, n=37; and control, n=20.	Children were evaluated by learning (Rey) and psychological (Digit, Code, Letter Concealing, and Symbol) tests. Children with OSAS and primary snoring

				had significantly worse performance in learning and memory when compared to controls (P=0.011).
Perez-Chada et al, 2007 [121]	Population-based, cross-sectional survey	IV	2884 students (mean age: 13.3 ± 1.5 years)	A Spanish version of the Pediatric Daytime Sleepiness Scale (PDSS) questionnaire was administered. Parental reporting of snoring occurred in 511 subjects (23%); snoring was occasional in 14% and frequent in 9%. Frequent snorers had higher mean PDSS scores than occasional or nonsnorers (18 ± 5, 15.7 ± 6 and 15.5 ± 6, respectively; P < 0.001). Reported snoring or apneas and the PDSS were significant of school failure failure (mathematics and language) after adjustment for age, gender, BMI, specific school attended, and sleep habits.
Suratt et al, 2007 [144]	Prospective cohort	III	56 children (6-12 y.o.) with adenotonsillar hypertrophy referred for suspected obstructive SDB	Sleep diary and wrist actigraphy for 6 consecutive days and nights. On day 7, general cognitive tests, memory tests, and continuous performance tests followed by attended polysomnography that night. Parents completed snoring and behavior questionnaires. Shorter mean time in bed for 6 nights and history of nightly snoring predicted lower scores for the vocabulary and similarities cognitive function tests. Children with mean time in bed of 557 min and without nightly snoring had vocabulary and similarities scores more than 1 standard deviation higher than children with mean time in bed of 521 minutes and nightly snoring. Shorter mean time in bed and the log of AHI also predicted lower vocabulary and similarities scores.
Suratt et al, 2006 [145]	Prospective cohort study	IV	114 children with adenotonsillar hypertrophy 6-12 y.o.)	Children underwent evaluation by questionnaires, general and memory cognitive tests, polysomnography. Vocabulary and similarities scores were affected significantly by the presence of snoring, race and sleep efficiency. Verbal memory and general memory scores were associated significantly with sleep latency while attention-deficit/hyperactivity disorder summary and hyperactive-impulsive summary were related significantly to sleep efficiency. AHI was a significant

				predictor of the vocabulary score.
Halbower et al, 2006 [146]	Cross-sectional study	IV	19 children with OSAS and 12 healthy controls (6-16 y.o.)	Subjects underwent polysomnography and neuropsychological assessment. Children with AHI > 8 episodes/h had significant deficits in IQ, verbal working memory and verbal fluency compared to controls.
Johnson & Roth 2006 [123]	Community-based survey	IV	1014 adolescents (13-16 y.o.)	Separate structured face to face diagnostic interviews of adolescents and parents were conducted. SDB was defined as report of loud snoring, gasping/choking or snorting, awakening with gasping or choking, or momentary periods of stopped or abnormal breathing occurring weekly. SDB was independently associated with excessive daytime sleepiness, poorer grades, and attention-deficit/hyperactivity disorder-inattention features.
Kurnatowski et al, 2006 [147]	Prospective cohort study	IV	87 children with adenotonsillar hypertrophy and sleep apnea aged 6-9 years; 34 children with adenotonsillar hypertrophy and sleep apnea aged 10-13 years; 104 healthy control children without adenotonsillar hypertrophy children.	Level of sensorimotor integration and perception processes, memory and learning abilities, language dysfunction were evaluated using: token test (TT), diagnosis test of brain dysfunction (DCS-test), Luria auditory verbal learning test (LAVLT) and Rey complex figure test (RCFT). In children 6-9 y.o., adenotonsillar hypertrophy was associated with memory problems, attention deficits, learning disability, language dysfunction, lower sensorimotor integration and perception. In children 10-13 y.o., adenotonsillar hypertrophy was related to memory problems and learning disabilities. Older children had more severe language dysfunction.
Blunden et al, 2005 [148]	Case-control study	IV	Snorers (n = 11); children with behavioral sleep problems (n = 13); snorers with behavioral sleep problems (n = 9); and controls (n = 31)	Subjects had psychological (Wechsler Abbreviated Scale of Intelligence, Children's Memory Scale; Test of Everyday Attention and Auditory Continuous Performance Test) and psychosocial assessment (Child Behavior Checklist). Snorers with or without sleep problems had significantly reduced intelligence and attention scores compared to children without snoring. By contrast, compared with children in the Snorers and control groups, Children

				with sleep problems with or without snoring had significantly reduced social competency, increased problematic behavior, and reduced memory scores compared to snorers without behavioral sleep problems or controls. Children with both snoring and behavioral sleep problems had overall more deficits than children in all other groups.
Carvalho et al, 2005 [149]	Case-control study	IV	79 children with SDB; 468 children with nonrespiratory sleep disorders; 633 normal control children. All children attending school in Brazil either in the morning or in the afternoon due to shortage of academic facilities.	Assessment of cognition. First grade morning students with SDB had 8.04 higher odds for cognitive dysfunction than control children. For children with SDB, second and third grade morning students had higher odds for cognitive dysfunction than those attending school in the afternoon (OR 3.69 and 4.07, respectively).
Ng et al, 2005 [150]	Cross-sectional telephone questionnaire survey in a community	IV	3047 children (6-12 y.o.)	Poor academic results were associated with presence of witnessed sleep apnea.
Beebe et al, 2004 [151]	Case-control study	III	32 snorers (6-12 y.o.) referred for polysomnography and 17 control subjects	Only snorers underwent polysomnography. Intelligence, verbal memory, processing speed, attention and executive functions were evaluated in all participants. Parents and teachers completed behavior questionnaires. Sleep was assessed by parents' response to questionnaires and polysomnography. Pediatric OSAS was associated with reduced verbal fluency and visual attention and parent-reported behavior problems and deficits in executive function. There was association of OSAS with impulse control and teacher-reported behavior and executive function. in particular, many tests of attention and executive functioning failed to yield group effects. No significant associations were found between measures of neuropsychological functioning and polysomnography indices.
Kennedy et al, 2004 [152]	Case-control study	IV	13 children with snoring and 13 children without snoring	Evaluation of neurocognitive function and polysomnography were performed. Mean AHI in snorers was 0.6 epiosdes/h. Compared to non-snorers, snorers had

				lower mean verbal IQ scores, global IQ scores, selective attention scores, sustained attention scores and mean memory index. Severity of neurocognitive deficits was associated with oxygen desaturations (≥ 3%), obstructive hypopneas with ≥ 3% oxygen desaturations, and respiratory arousals.
O'Brien et al, 2004 [153]	Prospective, population-based cohort study	I	299 children (5-7 y.o.) from public schools	Polysomnography and a battery of neurobehavioral and neurocognitive tests (Conners' parents rating scale, CBCL, DAS, NEPSY) were performed. Primary snoring (history of snoring, obstructive apnea index <1 episode/h, AHI <5 episodes/h, no gas exchange abnormalities): n=87; control subjects (no history of snoring, obstructive apnea index <1 episode/h, AHI <5 episodes/h, no gas exchange abnormalities): n=31. Children with primary snoring performed worse on measures related to attention, social problems, and anxious/depressive symptoms. Overall cognitive abilities and certain language and visuospatial functions were significantly lower for the group with primary snoring than for the control subjects.
O'Brien et al, 2004 [154]	Case-control study	II	35 children with SDB and 35 controls	When compared to controls, children with SDB had significantly lower mean scores on the Differential Ability Scales for General Conceptual Ability and for the Non-verbal Cluster. Children with SDB had significantly lower scores than controls on the NEPSY attention/executive function domain (visual attention and executive function) and on phonological processing. This subtest measures phonological awareness, a skill that is critical for learning to read. No differences in behavior, as measured by the Child Behavior Checklist (CBCL) or the Conners' Parent Rating Scale, were found between the two groups. Using a novel algorithm to assess sleep pressure children with SDB were found to be significantly sleepier than controls. Total arousal index was negatively correlated with neurocognitive abilities.
O' Brien et al, 2004 [155]	Prospective cohort study	IV	199 children	Children underwent polysomnography

				and neurocognitive testing. A sleep pressure score with a cutoff value of 0.25 was defined previously based on a large cohort of children without and with snoring. Children with sleep pressure score ≥ 0.25 had significantly higher frequency of deficits in memory, language abilities, verbal abilities, and some visuospatial functions than subjects with lower sleep pressure score.
Urschitz et al, 2004 [125]	Prospective, population-based cohort	IV	1144 children from the third-grade classes of primary schools	Habitual snoring (snoring frequently or always) and impaired behavior were assessed using parental questionnaires. Nocturnal oximetry was performed at home. Poor academic performance was defined as grade 4-6 on a 6-point scale in mathematics, science, or spelling with grade 1 used for "outstanding"). Habitual snorers were re-evaluated 1 year later. Habitual snoring was significantly associated with hyperactive and inattentive behavior, daytime tiredness, and sleepiness independent of intermittent hypoxia. Habitual snoring was also significantly associated with bad conduct, emotional symptoms, and peer problems. Among habitual snorers, 51.8% performed poorly at school as compared to 31.5% of the non-snorers. At follow-up, hyperactive and inattentive behavior had significantly improved in children in whom habitual snoring had resolved.
Chervin et al, 2003 [156]	Cross-sectional study	IV	146 children from second and fifth grades of elementary schools in USA.	Subjects were evaluated by teachers' ratings and reading and math assessments at end of school-year. Risk for SDB was evaluated using the Pediatric Sleep Questionnaire, and socioeconomic status based on qualification for lunch assistance at school. Risk for SDB was associated with African-American race, low socioeconomic status and poor teacher ratings ($P < 0.01$), but not with assessment scores at end of school year ($P > 0.1$). In multiple regression models, poor school performance was independently predicted by low socioeconomic status ($P < 0.01$) but not by African-American race or SDB risk.
Goodwin et al, 2003 [126]	Population-based, cross-sectional study	IV	1494 (4-11 y.o.) children	A 13-question sleep habits screening

				questionnaire designed to assess the severity of sleep-related symptoms associated with SDB was administered. Snoring was present if parents reported their child snored loudly "frequently" or "almost always". Learning problems at school were associated significantly with the presence of snoring.
Shin et al, 2003 [128]	Population-based cross-sectional survey	IV	A total of 3,871 high school students (15-18 y.o.)	Prevalence of habitual snoring was 11.2%. Frequency of snoring increased significantly with BMI ($P < 0.001$), cigarette smoking ($P < 0.01$), prevalence of witnessed apnea ($P < 0.001$), and Epworth sleepiness scale score ($P < 0.001$). Children with low school performance had increased risk of habitual snoring compared to those with high school performance (OR 1.35; 95% CI 1.01-1.78).
Kaemingk et al, 2003 [157]	Prospective, population-based cohort	III	149 children (6-12 y.o.)	Home polysomnography was performed; intelligence, learning and memory, and academic achievement were evaluated and attentionwas rated by parents. AHI was negatively associated with immediate recall, full- scale IQ, performance IQ, and math achievement. Hypoxemia was related to lower performance IQ.
d. *Behavioral disorders (conduct problems, emotional lability, anxiety and depressive symptoms)*				
Author, year	**Type of Study**	**Class**	**Subjects**	**Methods and findings**
Perfect et al, 2013 [130]	Prospective, population-based cohort	I	263 children evaluated in preadolescnce and approximately 5 years later in adolescence	Polysomnography and neurobehavioral assessment were performed at two time points approximately 5 years apart. Behavior assessment scale for children-2(nd) Edition parent report form (BASC-PRF) and Self-Report of Personality (SRP), and the Adaptive Behavior Assessment System-2nd Edition (ABAS-2) were used. Compared to those who never had SDB, individuals with persistent SDB had significant odds and met more cutoff scores on the BASC-2-PRF externalizing problems composite (OR 3.29; 8.92% vs. 35.3%), behavioral symptoms index (OR 6.82; 7.4% vs. 35.3%) and hyperactivity subscale (OR 6.82; 11.1% vs. 41.2%). Greater difficulties were demonstrated for the group with persistent SDB (relative to

				never) on the ABAS-2 social domain (OR 3.39; 22% vs. 50%), and Communication (OR 4.26; 15% vs. 42.9%) and Self-Care subscales (OR = 2.97; 25.2% vs. 50%). Relative to subjects who never had SDB, subjects who developed SDB over the 5-year observation period had compromised adaptive skills as indicated by the BASC-2 PRF adaptive behavior composite (OR 3.34; 15.6% vs. 38.1%) and the ABAS-2 general adaptive composite (OR 2.83; 20.5% vs. 42.1%).
Bonuck et al, 2012 [158]	Prospective cohort study	IV	n = 9140 at 4 years of age and n = 8098 at 7 years of age	Parents' report on children's snoring, mouth breathing, and witnessed apnea at 6, 18, 30, 42, 57, and 69 months of age and completion of the Strengths and Difficulties Questionnaire at 4 and 7 years of age. The SDB clusters predicted approximately 20% to 100% increased odds of problematic behavior, after controlling for multiple potential confounders.
Bourke et al, 2011 [159]	Cross-sectional study	IV	136 children (7-12 y.o.)	Children evaluated by nocturnal polysomnography [primary snoring (n=59), mild OSAS (n=24), moderate/severe OSAS (n=18), and controls (n=35)] the Child Behavior Checklist (CBCL) and the Behavior Rating Inventory of Executive Function (BRIEF). SDB groups had significantly higher ratings compared to the control group on the Withdrawn/Depressed subscale; primary snoring and mild OSAS groups had elevated scores relative to controls on somatic complaints. OSAS groups had significantly elevated scores on the aggressive behavior and rule-breaking behavior subscales as compared to controls.
Owens et al, 2008 [160]	Retrospective, cohort study	IV	235 children (3-18 y.o.) undergoing overnight polysomnography for symptoms of SDB	History of behavioral, emotional, and academic problems and Child Behavior Checklist (CBCL) scores were identified. 56% of subjects were overweight or at risk for overweight, 36% were short sleepers, and 49% had at least 1 additional sleep diagnosis. 47% had history of behavioral problems and 23% had reported diagnosis of attention-

				deficit/hyperactivity disorder. There were no significant differences in CBCL scores based on SDB severity. Increased weight was associated with increased internalizing CBCL scores (P = 0.003); short sleepers were more likely to have elevated externalizing scores (P < 0.001). The strongest predictor of adverse behavioral outcomes was the presence of at least 1 additional sleep diagnosis (P < 0.001).
Mulvaney et al, 2006 [161]	Prospective, population-based cohort study	III	403 children from the community (6-12 y.o.)	Overnight unattended in-home polysomnography was used to assess sleep and breathing and the Child Behavior Checklist and the Conners' Parent Rating Scales-Revised were used to assess behavior. Prevalence rates for attention, cognitive problems, aggression, oppositional behavior, and social problems were greatest for subjects with high respiratory disturbance index (RDI). Prevalence for internalizing behaviors and hyperactivity was not higher for those subjects with high RDI.
O'Brien et al., 2004 [153]	Population-based cross-sectional study	IV	299 children (5-7 y.o.) from public schools	Polysomnography and a battery of neurobehavioral and neurocognitive tests (Conners' parents rating scale, CBCL, DAS, NEPSY) were performed. Primary snoring (history of snoring, obstructive apnea index <1 episode/h, AHI <5 episodes/h, no gas exchange abnormalities): n=87; control subjects (no history of snoring, obstructive apnea index <1 episode/h, AHI <5 episodes/h, no gas exchange abnormalities): n=31. Children with primary snoring performed worse on measures related to attention, social problems, and anxious/depressive symptoms. Overall cognitive abilities and certain language and visuospatial functions were significantly lower for the group with primary snoring than for the control subjects.
Rosen et al, 2004 [162]	Prospective cohort study	III	829 children (8-11 y.o.) with term or preterm (<37 weeks' gestation) birth status	Home, unattended overnight recordings of airflow, respiratory effort, oximetry, and heart rate. Children evaluated by the Child Behavioral Checklist and the Conners Parent Rating Scale-Revised:Long. 5 % of children had

				OSAS, 15% had primary snoring. Children with SDB had significantly elevated problem scores in the following domains: externalizing, hyperactive, emotional lability, oppositional, aggressive, internalizing, somatic complaints, and social problems.
Chervin et al, 2003 [163]	Cross-sectional survey	IV	872 children (2-14 y.o.) at two general clinics	Conduct Problem Index (CPI) and Hyperactivity Index based on Conners Parent Rating Scale (CPRS-48) were used. Bullying and other aggressive behaviors were 2-3 times more prevalent among 114 children at high risk for SDB than among the remaining children. Significant association was demonstrated between high CPI and SDB scores (P <0.0001).
Gottlieb et al, 2003 [127]	Population-based, cross-sectional survey	IV	3019 (5 y.o.) children	A parent-completed questionnaire was used to identify snoring and other SDB symptoms and the presence of daytime sleepiness and problem behaviors. SDB was defined as frequent or loud snoring; trouble breathing or loud, noisy breathing during sleep; or witnessed sleep apnea. Children with SDB symptoms were significantly more likely to have parent-reported daytime sleepiness (OR= 2.2; 95% CI 1.7 – 2.8) and hyperactivity (OR=2.5; 95% CI 2.0-3.0), inattention (OR=2.1; 95% CI 1.7-2.6), and aggressiveness (OR=2.1; 95% CI 1.6-2.6).
Enuresis. somatic growth delay or growth failure				
a. *Enuresis*				
Author, year	**Type of Study**	**Class**	**Subjects**	**Methods and findings**
Jeyakumar et al, 2012 [164]	Systematic review	-	Pediatric studies from 1980 to 2010 on the association of SDB with enuresis and the effects of adenotonsillectomy were reviewed. 14 studies were reviewed including 3,550 children (age 18 months-19 years) with SDB, of whom one-third (n = 1,113) had a diagnosis of enuresis; in 7 studies (n =1,360) frequency of enuresis was evaluated also post-adenotonsillectomy (median follow-up of 6 months; age range of 2-18 years).	Preoperative prevalence of enuresis was 31% and postoperative prevalence was 16% (P = 0.0002). Most studies did not separate primary from secondary enuresis. Some subjects probably had age-appropriate enuresis.
Alexopoulos et al, 2014 [165]	Hospital-based, retrospective cohort study	IV	525 children (≥ 5 y.o.; 7.5 ± 2.2 y.o.) with snoring who were referred for polysomnography over 12 years were	Median obstructive AHI (10^{th}-90^{th} percentiles) was 1.9 (0.4-7.3) episodes/h. Three hundred and fifty five children

			reviewed.	(67.6%) had primary monosymptomatic nocturnal enuresis and 87 (16.6%) had moderate-to-severe OSA. There was no interaction between enuresis and gender regarding the association with moderate-to-severe OSA (P>0.05). Enuresis was associated significantly with presence of moderate-to-severe OSAS after adjustment for tonsillar hypertrophy, obesity, gender and age [adjusted OR = 1.92 (1.08-3.43); p=0.03]. Presence of NE had high sensitivity (78.2%) and low positive predictive value (19.2%) for detecting moderate-to-severe OSA and low specificity (34.5%) and high negative predictive value (88.8%) for ruling it out.
Su et al, 2011 [166]	Population-based, cross-sectional study	IV	6147 (3032 girls); 6-11 y.o.	Parents completed a questionnaire on SDB symptoms. Children at high risk of OSAS, along with a randomly selected low-risk group underwent overnight polysomnography. Overall prevalence of enuresis (at least 1 wet night/month) was 4.6% (6.7% of boys and 2.5% of girls). Prevalence of enuresis was not greater in children with OSAS, but it increased in parallel with OSAS severity in girls only.
Barone et al, 2009 [167]	Case-control study	III	Case patients (5-15 y.o. referred for suspected OSAS) were recruited from a sleep disorders center (n = 149), and control subjects were recruited from a general pediatric practice (n = 139)	Only case patients underwent polysomnography. Logistic regression demonstrated that primary monosymptomatic nocturnal enuresis was significantly associated with OSAS [OR (95% CI) 12.599 (2.738–57.975)] after adjustment for other confounding variables including adiposity.
Sans Capdevila et al, 2008 [168]	Population-based, cross-sectional study	IV	17646 children (5-7 y.o.) from the community	Questionnaire completed by parents; nocturnal polysomnography in 378 children. Enuresis (≥ 3 nights/week) was present in 26.9% of children with habitual snoring and 11.6% of children without snoring (P < 0.00001). Enuresis among 378 children with habitual snoring did not correlate with the magnitude of sleep respiratory disturbances.
Alexopoulos et al, 2006 [169]	Population-based, cross-sectional study	IV	1821 children (5-14 y.o.; 896 girls) attending 6 randomly selected schools in a city in central Greece	Parents completed a questionnaire regarding the symptoms of SDB and the presence of nocturnal enuresis (≥1 night/week). 135 (7.4%) were snoring

				more frequently than 3 nights/week (habitual snorers). Habitual snorers had history of primary nocturnal enuresis more often than non-habitual snorers [7.4% vs. 2%; OR (95% CI) 4.00 (1.93 - 8.32)]. The association of primary nocturnal enuresis with habitual snoring remained significant after adjustment for age and sex [OR 3.54 (1.68-7.44)].
Brooks et al, 2003 [170]	Prospective cohort study	IV	90 boys and 70 girls (≥ 4 y.o.) referred for polysomnography due to suspected SDB	Children with a respiratory disturbance index ≤1 episode/h had a significantly lower prevalence of enuresis (17%) than did children with a respiratory disturbance index >1 episode/h (47%) ($P < 0.05$).
b. *Somatic growth delay or growth failure*				
Author, year	**Type of Study**	**Class**	**Subjects**	**Methods and findings**
Hsu et al, 2013 [171]	Retrospective, cohort study	IV	161 children (mean age, 7.0 ± 3.4 years; 78% boys) with OSAS who underwent adenotonsillectomy.	All patients had polysomnography before and after surgery. Children were classified into underweight, normal weight, overweight and obese, based on age and gender corrected body mass index. Postoperatively, all four groups significantly improved regarding AHI and SpO_2 nadir. 49.1% of all children (79/161) had residual OSAS (AHI ≥ 1 episode/h). The incidence of residual OSAS in the obese group was 75%, which was significantly higher compared to the other three groups ($P<0.01$). 54% (13/24) of the underweight children attained normal weight status within 6 months after surgery.
Bonuck et al, 2009 [172]	Systematic review and meta-analysis	-	20 cohort studies describing changes in weight, height, IGF-1 and/or IGFBP-3 serum-levels as z-scores, percentiles or raw data following adenotonsillectomy were reviewed. Studies ranged in numbers of participants from 14 to 204 children and ages of 5 months to 15.8 years with follow-up of 1 month to 3 years.	6 of 20 studies reported growth failure in a proportion of their participants. Results of meta-analysis regarding postoperative changes compared to preoperative values were reported. Standardised height (10 studies; n=363): pooled standardised mean differences (SMD) = 0.34 (95% CI 0.20-0.47); standardised weight (11 studies; n=390): pooled SMD = 0.57 (95% CI 0.44-0.70); IGF-1 (7 studies; n=177): pooled SMD = 0.53 (95% CI 0.33-0.73); IGFBP-3: (7 studies; n=177): pooled SMD = 0.59 (95% CI 0.34 to 0.83).
Decreased quality of life				

Garetz et al, 2015 [173]	Multicentre, single-blind, randomised, controlled trial	I	464 children (5-9 y.o.) with OSAS randomly assigned to early adenotonsillectomy (median baseline obstructive AHI 4.8 episodes/h) or watchful waiting (median baseline obstructive AHI 4.5 episodes/h). OSAS was defined as an obstructive AHI ≥2 episodes/h or an obstructive apnea index ≥1 episode/h. The Pediatric Quality of Life inventory, the Sleep-Related Breathing Scale of the Pediatric Sleep Questionnaire, the 18-item Obstructive Sleep Apnoea QoL instrument, and the modified Epworth Sleepiness Scale were completed before adenotonsillectomy and at 7 months postoperatively.	Greater improvements regarding most measures of quality of life and symptom severity were demonstrated in the early adenotonsillectomy group than in the watchful waiting arm. There was weak correlation between improvement in polysomnography indices and changes in quality of life or symptom severity measures. Baseline OSAS severity did not influence the association between quality of life or symptom severity measures and treatment arm.
Baldassari et al, 2008 [174]	Meta-analysis	-	10 studies including 1470 children: 562 children with OSAS, 815 healthy children, and 93 children with juvenile rheumatoid arthritis	In three studies, 193 patients with OSAS, 93 children with juvenile rheumatoid arthritis and with 815 healthy children were compared using the Child Health Questionnaire (CHQ). Children with OSAS had poorer scores in 8 of 12 CHQ subscale scores than controls. Children with OSAS had poorer scores in the parental impact-emotional subscale than healthy controls. Children with OSAS were similar to patients with juvenile rheumatoid arthritis regarding quality of life scores. In seven studies, 369 children with OSAS underwent adenotonsillectomy and the OSA-18 total and subscale scores improved significantly ($P < 0.0001$). Improvement persisted at long-term follow-up.

Question 2.2. Which conditions frequently co-exist with obstructive SDB (possibly common pathogenetic mechanisms) and may potentially improve with treatment of SDB?				
a. *Recurrent otitis media or history of tympanostomy tube placement*				
Author, year	**Type of Study**	**Class**	**Subjects**	**Methods and findings**
Aydemir et al, 2011 [175]	Population-based, cross-sectional study	IV	423 children (7-12 y.o.) attending three primary schools in Turkey.	An ear, nose and throat examination and tympanometry were performed and a questionnaire was completed by parents. Type B or C2 tympanograms were defined as diagnostic of otitis media with effusion (OME). The prevalence of OME was 16%. Presence of OME was significantly related to frequency of upper respiratory tract infections and

				acute otitis media during the previous year, class size and snoring. Presence of OME was not associated with allergic symptoms, kindergarten years, duration of breast-feeding, parental smoking, presence of domestic animals, family size, type of home heating, parental educational level or monthly income.
Gozal et al, 2008 [176]	Cross-sectional, population-based study	IV	16,321 children (51.2% boys; 18.6% African American; mean age of 6.2 ± 0.7 years) attending the public schools in Louisville, KY.	Questionnaires were collected from parents which the presence of habitual snoring, recurrent otitis media, and the need for tympanostomy tube insertion. Of all children, 1844 (11.3%) had habitual snoring (53% boys; 25.9% African American); of 1844 habitual snorers, 827 (44.8%) had history of recurrent otitis media and 636 (34.4%) had history of tympanostomy tube insertion. Among the 14,477 non-snoring children, recurrent otitis media was reported in 4247 (29.3%) and history of tympanostomy tube placement in 1969 (13.6%); odds ratio 1.95; 95% confidence interval 1.77-2.16) for recurrent otitis media and odds ratio 2.19; 95% confidence interval 1.98-2.43) in children with snoring compared to those without snoring.
Caylan et al, 2006 [177]	Cross-sectional, population-based study	IV	1,077 children (5-12 y. o.) were examined for otitis media with effusion (OME).	OME prevalence was 11.14%. Young age, kindergarten/daycare attendance, low economical status, mother's working status, history of snoring and acute otitis media, antibiotic use in the previous 3 months and active upper respiratory tract infection were risk factors for OME.
Martines et al, 2006 [178]	Population-based, prospective	IV	2097 children (5-14 y. o.)	Otoscopy and tympanometry were performed at 3-monthly intervals beginning at term date to diagnose otitis media with effusion (OME). Standardized questionnaires were completed and skin tests were performed. Prevalence of OME was 6.8% and it was associated with atopy (odds ratio 12.67; 95% confidence interval 8.78-18.27). Snoring ($P<0.0001$), previous history of acute otitis media ($P<0.001$) and recurrent upper respiratory tract infections ($P<0.0001$) were aslo associated

				significantly with presence of OME.
b. *Recurrent wheezing or asthma*				
Author, year	**Type of Study**	**Class**	**Subjects**	**Methods and findings**
Bhattacharjee et al, 2014 [179]	Retrospective, cohort study	II	13,506 children with asthma who underwent adenotonsillectomy and 27,012 age-, sex-, and geographically matched children with asthma without history of adenotonsillectomy all of whom were included in a database of privately insured patients in the USA	Asthma outcomes during one year prior to adenotonsillectomy were compared to those during one year following adenotonsillectomy. Adenotonsillectomy was associated with significant reductions in acute asthma exacerbations (30.2%; 95% CI: 25.6%-34.3%; P <0.0001), acute status asthmaticus (37.9%; 95% CI: 29.2%-45.6%; P <0.0001), asthma-related emergency room visits (25.6%; 95% CI: 16.9%-33.3%; P <0.0001), and asthma-related hospitalizations (35.8%; 95% CI: 19.6%-48.7%; p = 0.02). Adenotonsillectomy was also accompanied by significant reductions in prescription refills of bronchodilators (16.7%; 95% CI: 16.1%-17.3%; P <0.001), inhaled corticosteroids (21.5%; 95% CI: 20.7%-22.3%; P <0.001), leukotriene receptor antagonists (13.4%; 95% CI: 12.9%-14.0%; P <0.001), and systemic corticosteroids (23.7%; 95% CI: 20.9%-26.5%; P<0.001). Such improvements in asthma outcomes were not reported in controls over the same two-year follow-up period.
Ross et al, 2012 [180]	Prospective, cohort study	III	108 subjects (mean age, 9.1 ± 3.4 years; Range 4-18 y.o.; 45.4% African-American; 67.6% male) from an asthma clinic. obesity and SDB were common, affecting 42.6% and 29.6% of subjects, respectively.	Children underwent physiological, anthropometric, and biochemical assessment and polysomnography. Asthma severity was determined at 1 year of treatment based on level of controller medication, symptom severity, and health care utilization. After adjustment for obesity, race, and gender, children with SDB had a 3.62-fold increased odds of having severe asthma at 1 year (95% CI 1.26-10.40). Obesity was not associated with asthma severity.
Kheirandish-Gozal et al, 2011 [181]	Retrospective, cohort study	IV	92 children with poorly controlled asthma (3-10 y.o.) followed in a specialty asthma center over a 3-year period.	Children were referred for polysomnography and adenotonsillectomy if OSAS was present (AHI >5 episodes/h). Mean frequency of asthma exacerbations was 3.4 ± 0.4 episodes/year. OSAS was diagnosed in 58 patients. 35 of them

				were followed at 1-year and they had significant improvements in the number of exacerbations/year, weekly rescue medication use, symptom scores, and lung function (FEV_1) as compared to children without OSAS.
Malakasioti et al, 2011 [182]	Systematic review	-	13 studies including 27,453 children (0-18 y.o.)	Most reports have been based on symptom questionnaires for the diagnosis of SDB. A signifant association between obstructive SDB and recurrent wheezing/asthma was demonstrated in all studies i.e. increased prevalence of snoring or elevated AHI among children with history of wheezing or physician-diagnosed asthma. In a community-based cohort, subjects with increased AHI had increased likelihood for wheezing.
c. *Metabolic syndrome*				
Author, year	**Type of Study**	**Class**	**Subjects**	**Methods and findings**
Nobili et al, 2014 [183]	Retrospective, cohort study	IV	65 consecutive children with biopsy-proven nonalcoholic fatty liver disease (11.7 ± 2.1 y.o., 58% boys; BMI z score 1.93 ± 0.61)	OSAS was defined as AHI ≥ 1 episodes/h, and severe OSAS was defined as AHI ≥ 5 episodes/h. 60% of children with nonalcoholic fatty liver disease had OSAS, 55% had nonalcoholic steatohepatitis, and 34% had significant fibrosis; presence and severity of OSAS were associated with the presence of nonalcoholic steatohepatitis (OR 4.89; 95% CI 3.08-5.98; P = 0.0001), significant fibrosis (5.91; 3.23-7.42; P = 0.0001), and nonalcoholic fatty liver disease activity score (P = 0.029), independently of BMI, abdominal adiposity, metabolic syndrome, and insulin resistance. Presence of OSAS was associated with presence of the metabolic syndrome.
Nandalike et al, 2012 [184]	Case-control	III	28 girls with polycystic ovary disease (16.8 ± 1.9 y.o.; BMI z score 2.4 ± 0.4); 28 control females (17.1 ± 1.8 y.o.; BMI z score 2.4 ± 0.3); and 28 control males (age: 16.6 ± 1.6 y.o.; BMI z score 2.5 ± 0.5)	Prevalence of OSAS was higher in girls with polycystic ovary disease compared to control females (57% vs. 14.3%; P<0.01) and comparable to that of control males (57% vs. 75%; P=0.4). Girls with polycystic ovary disease had significantly higher prevalence of insulin resistance compared to control females and control males (71.4% vs.

				41.0% vs. 34.8%; P<0.05). Among girls with polycystic ovary disease, those with OSAS had significantly higher proportions of metabolic syndrome (56.3% vs. 8.3%; P=0.03), higher insulin resistance, elevated daytime systolic blood pressure, lower HDL and elevated triglycerides compared to those without OSAS.
de Sousa et al, 2011 [185]	Case-control study	III	14 obese adolescents with polycystic ovary disease and metabolic syndrome (15.7 ± 1.9 y.o.; BMI 36.2 ± 6.2 kg/m^2), 14 obese adolescents with polycystic ovary disease without metabolic syndrome (15.7 ± 1.1 y.o.; BMI 33.8 ± 6.2 kg/m^2), 19 healthy, obese adolescents without polycystic ovary disease or metabolic syndrome (15.3 ± 1.0 y.o.; BMI 34.4 ± 6.5 kg/m^2), and 14 healthy, normal-weight adolescents (15.4 ± 0.7 y.o.; BMI 21.1 ± 2.2 kg/m^2)	No significant differences among the four groups concerning AHI or % stages 3 and 4. Significant differences among the groups were found regarding SpO_2 (P = 0.04), % REM (P = 0.03), sleep-onset latency (P = 0.002), and sleep efficiency (P = 0.01).
Verhulst et al, 2007 [186]	Cross-sectional study	IV	104 overweight or obese subjects (44% boys; 58% prepubertal; 11.1 ± 2.6 y.o.; 69% obese).	Mean SpO_2 and SpO_2 nadir were independent, significant predictors of the presence of metabolic syndrome (OR 0.54 and 0.89, respectively).
Redline et al, 2007 [187]	Cross-sectional, population-based study	IV	270 adolescents (13.6 ± 0.7 y.o.)	After adjustment for age, race, gender, and preterm status, children with SDB had a 6.49 (95% CI 2.52- 16.70) increased odds of metabolic syndrome compared to children without SDB.
d. *Oral-motor dysfunction*				
Author, year	**Type of Study**	**Class**	**No. of subjects**	**Methods and findings**
Junqueira et al, 2010 [188]	Cross-sectional study	IV	346 subjects (2-16 y.o.) with history of mouth breathing (allergic rhinitis, adenoidal hypertrophy, allergic rhinitis with adenoidal hypertrophy; and/or functional mouth breathing).	Children underwent speech-language pathology evaluations for orofacial function (tongue and lip rest postures, tonus, articulation and speech, voice and language, chewing, and deglutition). The most common finding was the presence of orofacial myofunctional disorders. The most frequent orofacial myofunctional disorder identified in subjects with mouth breathing included: habitual open lips rest posture, low and forward tongue rest posture and lack of adequate muscle tone. The etiology of mouth breathing was not associated with the presence, type, or number of speech-language abnormalities.
Honaker et al, 2009 [140]	Cross-sectional study	IV	Age-, gender-, ethnicity, and maternal	Verbal skills and language

			education matched groups of children (1st to 3rd grades) with habitual snoring and normal overnight sleep studies (n=76), children with significant SDB (n=76) and non-snoring healthy controls (n=76).	neurodevelopment were assessed. Children with SDB had difficulties in processing verbal instructions of increasing linguistic complexity, and their ability of verbal concepts was decreased.
Lundeborg et al, 2009 [189]	Retrospective, cohort study	IV	67 children with adenotonsillar hypertrophy assigned to tonsillectomy (n=33) or partial tonsillectomy (n=34) in combination with adenoidectomy; 76 controls.	Oral motor function (chewing, swallowing, articulation, and voice) in children with adenotonsillar hypertrophy was evaluated by the Nordic Orofacial Test-Screening (NOT-S) before and 6 months after surgery. Most children in the study groups had oral motor problems preoperatively: snoring, open mouth position, drooling, masticatory, and swallowing problems. Postoperatively oral motor function in patients with adenotonsillar hypertrophy was similar to controls.
O' Brien et al, 2004 [154]	Cross-sectional study	IV	35 children with SDB diagnosed by polysomnography were matched for ethnicity, age, gender, maternal educational attainment, and maternal smoking, to healthy children without SDB.	Children with SDB had significantly lower mean scores on the Differential Ability Scales for General Conceptual Ability (similar to IQ) and for the Non-verbal Cluster. On the neuropsychology assessment battery (NEPSY), children with SDB scored significantly lower than the control group on the attention/executive function domain and two subtests within that domain, one measuring visual attention and the other executive function. Children with SDB had significantly lower scores than the controls on the NEPSY Phonological Processing (phonological awareness, a skill that is critical for learning to read).
Valera et al, 2003 [190]	Cross-sectional study	IV	73 children (3-6 y.o.); 44 with tonsillar hypertrophy and 29 controls.	Children underwent otorhinolaryngologic, speech pathologic and orthodontic assessment. Children with tonsillar hypertrophy had higher incidence of nasal obstruction, snoring, mouth breathing, apneas, nocturnal hypersalivation, itchy nose, recurrent tonsillitis and bruxism in children than controls. Speech pathologic assessment revealed higher incidence of open lip and lower tongue position, hypotonia of the upper and lower lips, tongue and buccinator muscle as well as impairment in mastication and deglutition. Orthodontic evaluation showed higher

				incidence of lower mandible position in relation to the cranial base, decrease in lower posterior facial height, transverse atresia of the palate, and dolicofacial pattern compared to controls.

Online Supplementary Table 3.

Step 3: Recognition of factors predicting long-term persistence of obstructive SDB

Question 3.1. Is there evidence from short-term controlled studies or long-term prospective studies regarding predicting factors of spontaneous resolution or long-term persistence of untreated obstructive SDB?				
Author, year	**Type of Study**	**Class**	**Subjects**	**Methods and findings**
Li et al, 2013 [191]	Prospective, population-based, cohort study	I	70 children with ages 6-13 years and a diagnosis of primary snoring in a previous community-based study evaluating the prevalence of OSAS were invited for repeat polysomnography 4 years later (mean age 14.7 ± 1.8 years; 60% boys).	OSAS was defined as obstructive AHI ≥ 1 episodes/h. Mean duration of follow-up was 4.6 ± 0.6 years. On repeat polysomnography, 26 subjects (37.1%) had progressed to OSAS and 5 (7.1%) of them had moderate to severe disease (OAHI ≥5 episodes/h). 22 (31.4%) children had persistent primary snoring and 18 (25.7%) had complete resolution of snoring with normal polysomnogram. Multivariate logistic regression analysis demonstrated that persistent overweight/obesity was a significant risk factor for the progression to OSAS (OR 7.95; 95% CI 1.43-44.09).
Marcus et al, 2013 [192]	Randomized controlled multicenter trial early adenotonsillectomy versus watchful waiting	I	464 (5-9 y.o.), 46% children in the watchful waiting group and 48% in the early treatment group were overweight or obese. Polysomnographic, cognitive, behavioral, and health outcomes were evaluated at baseline and at 7 months.	The two groups did not differ regarding change in the Developmental Neuropsychological Assessment from baseline to follow-up (P=0.16). There were significantly greater improvements in behavioral, quality-of-life, and polysomnographic outcomes and greater symptom reduction in the early-adenotonsillectomy group compared to the watchful-waiting group. Normalization of polysomnographic findings was observed in a larger proportion of children in the early-adenotonsillectomy group than in the watchful-waiting group (79% vs. 46%). In the watchful-waiting group, spontaneous OSAS resolution was more common in nonblack children (P <0.01), nonobese children (P <0.001), and

				children with a baseline AHI ≥4.7 episodes/h (P <0.001).
Goodwin et al, 2010 [193]	Prospective, population-based, cohort study	I	319 children had 2 polysomnograms at home approximately 5 years apart. The mean age at first evaluation was 8.5 years (range 6-12), and mean age at second assessment was 13.7 years (range 10-18).	SDB was defined as a respiratory disturbance index ≥1 episode/h associated with oxygen desaturation ≥3%. Body mass index percentiles were calculated. Incident SDB was more frequent in boys (OR 3.93; 95% confidence interval 1.41-10.90; P=0.008). Children with prevalent SDB were more likely to be boys (OR=2.48; P=0.006) and had a greater increase in body mass index percentile (OR 1.01; P=0.034). Children with prevalent SDB had 3.41 greater odds for development of obesity from baseline to follow-up compared to children with prevalent No SDB.
Li et al, 2010 [194]	Prospective, population-based, cohort study	III	45 children identified with mild OSAS (AHI 1-5 episodes/h) in a previous community-based study of subjects with ages 6-13 y.o. evaluating the prevalence of OSAS underwent repeat polysomnography 2 years later (mean age 14.7 ± 1.8 years; 60% boys).	In 13 of 45 (29%) children OSAS severity worsened (increase in obstructive AHI >2.38 episodes/h). Compared to children in whom OSAS severity did not worsen, the worsened OSAS group had greater increase in waist circumference, higher frequency of tonsillar hypertrophy at baseline and follow-up visits, and higher prevalence of habitual snoring at baseline and follow-up evaluations. Multivariate analysis demonstrated that change in obstructive AHI was associated significantly with age at baseline (P = 0.009), male gender (P<0.001), presence of tonsillar hypertrophy at baseline (P = 0.001), change in waist circumference (P = 0.002) and persistent tonsillar hypertrophy over the 2-year period (P<0.001).
Hultcrantz et al, 2009 [195]	Prospective, population-based cohort	III	The initial cohort included 4-year children in Enköping (Sweden. All children born over 16 consecutive months were included (n=615). 509 children took part in the 6-year evaluation and 393 (78.4%) of them continued participated at the age of 12 years.	SDB was tracked by completion of a questionnaire at ages 4, 6 and 12. Clinical examination, polygraphy (at ages 4 and 12) and orthodontic evaluation were completed for all chidren snoring regularly and for a subgroup of children without snoring. OSAS was defined as AHI ≥ 1 episode/h or Obstructive Desaturation Index ≥ 1 episode/h. Of 393 children with completed questionnaires, 27 snored regularly and

				231 did not snore at all at the age of 12. The prevalence of OSAS decreased from 3.1% at the age of 4 years to 0.8% at the age of 12 years and the severity decreased from a mean AHI 14.8 episodes/h at the age of 4 years to a mean AHI of 1.95 episodes/h at the age of 12 years. The minimum estimated prevalence of snoring regularly was 4.2% at 12 years compared to 5.3% at 4 years. The odds for a child who snored regularly at 4 or 6 years to be snoring regularly also at age 12 compared to a non-snoring child was 3.7 with 95% confidence interval 2.4-5.7. 63 children had undergone adenotonsillectomy, adenoidectomy or tonsillectomy due to snoring by age 12 years. 17 of them snored regularly at the age of 12 years. The dental arch was narrower in the children snoring regularly at 4, 6 and 12 years compared to children without snoring. Cross-bites were more common in children with snoring than children without snoring.

Online Supplementary Table 4.

Step 4: Objective diagnosis and assessment of obstructive SDB severity

Question 4.1. What are the indications for in-hospital video-polysomnography, polysomnography and polygraphy?				
a. *Indications for in-hospital polysomnography and polygraphy (airflow monitoring, chest and abdominal wall movements, pulse oximetry) in the context of obstructive SDB*				
Author, year	**Type of Study**	**Class**	**Subjects**	**Methods and findings**
Marcus et al, 2012 [9]	Clinical Practice Guideline	-	-	350 relevant articles
Aurora et al, 2011 [8]	Practice parameters paper	-	-	-
Roland et al, 2011 [196]	Clinical Practice Guideline	-	-	199 relevant articles
Wise et al, 2011 [7]	Systematic review	-	-	243 evidentiary papers were analyzed and summarized.

Question 4.2. What are the cut-off values of cardiorespiratory parameters in polysomnography or polygraphy for the diagnosis of OSAS?

a+b. *Scoring of respiratory events-central apnoea index*				
Author, year	**Type of Study**	**Class**	**Subjects**	**Methods and findings**
Baldassari et al, 2011 [197]	Retrospective cohort study	IV	15 children (67.7 ± 62.7 m.o.) who underwent adenotonsillectomy for OSAS and had both preoperative and postoperative polysomnography with central apnea index > 1 episode/h on preoperative polysomnography were included in the analysis out of 101 children with OSAS.	Central apnoea index was 1.1-11.1 episodes/h. Central apnea index decreased from 3.9 ± 2.9 episodes/h to 1.9 ± 4.8 episodes/h, postoperatively (P = 0.008). Ninety percent of subjects with central apnea index 1-5 episodes/h had postoperative central apnoea index < 1 episode/h. There was also significant decrease in the obstructive AHI (P = 0.004).
O'Driscoll et al, 2009 [198]	Cross-sectional study	IV	53 children (28 male; 7-12 y.o.) with symptoms of SDB; 21 age-matched healthy controls (8 male).	Participants underwent nocturnal polysomnography and continuous blood pressure monitoring. Central apnoeas were classified as spontaneous or movement-induced (following movement or sigh). Beat-by-beat mean arterial pressure and heart rate were analyzed over the duration of central apnoeas. Movement-induced, but not spontaneous central apneas were significantly more frequent in children with mild or moderate/severe OSAS than in healthy controls (P < 0.05 for both). Movement-induced central apneas were associated with significantly larger mean arterial pressure and heart rate changes during the event compared with spontaneous central apnoeas.
c+d. *Polysomnography parameters in children without symptoms of obstructive SDB*				
Author, year	**Type of Study**	**Class**	**Subjects**	**Methods and findings**
Scholle et al, 2012 [199]	Cross-sectional study	III	209 healthy German children (1-18 y.o.)	With increasing age, a decrease was seen in: EEG arousal index, index of total EEG arousals, respiratory arousal index, index of total leg movements, and leg movements with EEG arousals (P < 0.05).
Scholle et al, 2011 [200]	Cross-sectional study	III	209 healthy German children (1-18 y.o.)	One-night polysomnography was performed in 16 laboratories. Normative values of cardiorespiratory parameters were summarized. No obstructive and mixed apneas were identified Hypopneas and central apneas (≥20 sec) were infrequent. In addition, oxygen desaturations or arousals accompanying central apneas were rare.
Tapia et al, 2008 [201]	Cross-sectional study	IV	68 healthy children 8-18 y.o. (13 ± 3	Polysomnography was performed and

			y.o. ; Tanner 1-5)	scored according to the 2007 AASM rules. Median AHI was 0.1 episodes/h (range: 0-1.2 episodes/h). The median percentages of total sleep time with SpO_2 < 92% were 0.1 (0-4.2)%, and with end-tidal CO_2 > 50 mmHg was 0.1 (0-88.6)%. 32 subjects were aged 13-18 years, (Tanner 3-5). The difference between AHI scored by pediatric AASM rules (median AHI 0 [0-0.9] episodes/h) and adult AASM rules (median AHI 0 [0 - 0.5] episodes/h) was statistically significant (P = 0.043), but not clinically significant.
Saito et al, 2007 [202]	Prospective cohort study	III	232 children (1.4-10 y.o.) with symptoms indicative of SDB and 25 healthy children as controls.	All children had nocturnal oximetry and 86 of them underwent adenotonsillectomy and follow-up oximetry. Mean oxygen desaturation index (≥3%-ODI3) in controls was 0.74 episodes/h and standard deviation 0.65. Also mean oxygen desaturation index (≥4%-ODI4) was 0.21 and standard deviation 0.29. Improvements in ODI3 and ODI4 after adenotonsillectomy correlated significantly with preoperative values. 95% of subjects with ODI3 ≥ 3.5 episodes/h and/or ODI4 ≥ 1.5 episodes/h had improvement in the respective indices > twice the standard deviation in controls.
Verhulst et al, 2007 [203]	Cross-sectional study	IV	60 children without symptoms of SDB: 38 normal weight, 6 overweight, and 16 obese with a mean age of 11.7 ± 2.6 years	The mean central apnea index was 0.85 ± 1.06 episodes/h (median=0.56; range: 0.00–5.53). The mean obstructive apnea index was 0.06 ± 0.16 episodes/h (median=0.00; range: 0.00–0.87). The mean obstructive AHI was 0.08 ±0.17 episodes/h, (median=0.00; range=0.00–0.87). Subjects in the overweight group (n=22) had a lower SpO_2 nadir (90.8 ± 2.7% vs. 92.4 ± 2.6; P=0.01) and a higher oxygen desaturation index (1.3 ± 1.3 episodes/h vs. 0.4 ± 0.4 episodes/h; P=0.0002) compared to children with normal weight.
Montgomery-Downs et al, 2006 [204]	Retrospective analysis of data from 2 large community-based studies	IV	542 healthy children with ages ranging from 3.2 to 8.6 years	Average obstructive apnea index was 0.03 episodes/h for 3- to 5-year-old children and 0.05 episodes/h for ≥ 6-year-old children, whereas central apnoea index was 0.82 and 0.45 episodes/h, respectively. AHI differs according to body position. Twenty

				percent of all subjects had end tidal carbon dioxide values of >45 mm Hg, and 2.2% had values >50 mm Hg at least 50% of total sleep time.
Traeger et al, 2005 [205]	Retrospective cross-sectional analysis of a prospective cohort study	IV	66 children (2–9 y.o.) with normal growth and development	Respiratory events included a central apnoea index of 0.08 ±0.14 episodes/h, obstructive apnoea index of 0.01 ± 0.03 episodes/h, and obstructive hypopnoea index of 0.3 ±0.5 episodes/h. The baseline arterial oxygen saturation (SpO2) was 97 ± 1%, with a nadir of 92 ± 3%.
Fukumizu et al, 2004 [206]	Cross-sectional study	IV	19 healthy children (3 m.o.-7 y.o.)	Children underwent polysomnography with respiratory inductive plethysmography. Participants were divided into two age groups: <15 m.o. and >15 m.o. The frequency of central respiratory pauses ≥10 s increased with age, whereas the frequency of gross body movements and sighs decreased. Isolated central respiratory pauses occured more frequently during REM sleep than during non-REM sleep. The frequency of both sighs and gross body movements that followed central respiratory pauses was higher during REM than during non-REM sleep. The sum of central respiratory events preceded by sighs or gross body movements accounted for about 75% of all central apneas.
Uliel et al, 2004 [207]	Cross-sectional study	IV	70 healthy, normal children and adolescents. Age ranged from 1 to 15 years (mean age 8.02 ± 4.57 years).	The mean number of obstructive apnoeas per hour of sleep was 0.37 (1 to 5 apneas per child per study. The mean number of central apnoeas per hour of sleep was 0.4 (median, 0.33; 97.5 percentile, 0.9). The mean SpO2 was 97.2 ± 0.8% with SpO_2 nadir of 94.6 ± 2.2%. Peak end-tidal CO_2 > 45 mm Hg occurred for 1.6 ± 3.8% of total sleep time. The normal limits recommended: obstructive apnoea index, 1; central apnoea index, 0.9; baseline SpO_2, 92%; and peak end-tidal CO_2 > 45 mm Hg for < 10% of total sleep time.
Goh et al, 2000 [208]	Cross-sectional study	IV	20 children with OSAS and 10 controls	Spontaneous arousals, but not respiratory-related arousals, were more frequent during non-REM than REM sleep; Spontaneous arousals: 3 ± 2.4

				versus 1 ± 0.2 episodes/h, P <0.002; respiratory arousals: 1 ± 1.4 versus 3 ± 1.6 episodes/h, NS). Arousal index was 11 ± 4 episodes/h in the OSAS group and 5 ± 2 episodes/h in the control group, P < 0.001.
Acebo et al, 1996 [209]	Cross-sectional study	IV	Healthy boys (n=23; mean age 13.3 ± 2.1 years), girls (n=22; mean age 13.8 ± 1.8 years), men (n=23; mean age 22.2 ± 1.5 years), and women (n=24; mean age 22.4 ± 1.8 years) with body mass index <27 kg/m^2 were recruited.	Nocturnal polysomnography was performed and cephalometric measurements were obtained from lateral skull radiograph. Slow-wave sleep and REM latency decreased with age and transient arousals increased with age. Sleep-related breathing variables did not change with age or gender. Small and statistically significant differences in arterial oxygen saturation of hemoglobin were found according to gender (lower values in male subjects) and respiratory disturbance index duting non-REM sleep (higher in male subjects). There were also Differences in cephalometric measures according to age and gender.
Marcus et al, 1992 [210]	Cross-sectional study	IV	50 normal children (mean age 9.7± 4.6 years, range 1.1-17.4 years)	Children had 0.1 ± 0.5 episodes/h (range 0 to 3.1) obstructive apneas per hour of total sleep time. Of all children, 30% had central apneas ≥ 10 seconds in duration. Peak end-tidal CO2 was 46 ± 4 mmHg (range 38 to 53 mmHg). The SpO_2 nadir was 96 ±2% (range 89 to 98%).
e. *OSAS Definition 1*				
Author, year	**Type of Study**	**Class**	**Subjects**	**Methods and findings**
Marcus et al, 2013 [192]	Randomized controlled multicenter trial early adenotonsillectomy versus watchful waiting	I	464 (5-9 y.o.) with obstructive AHI ≥2 episodes/h or an obstructive apnoea index ≥1 episode/h; 46% children in the watchful waiting group and 48% in the early treatment group were overweight or obese.	At 7 months, significantly more children in the early intervention group (79%) had a postoperative obstructive AHI < 2 episodes/h and an obstructive apnoea index,1 episode/h compared to the watchful waiting group (46%) (P< 0.001).
f. *OSAS Definition 2*				
Author, year	**Type of Study**	**Class**	**Subjects**	**Methods and findings**
Sedky et al, 2014 [131]	Meta-analysis	-	*Relationship between SDB and ADHD symptomatology:* 18 studies with 1113 children in the clinical group (874 had SDB and were examined for ADHD symptoms; 239 had ADHD and were examined for SDB) and 1405 in the control-group.	*Relationship between SDB and ADHD symptomatology:* Medium relationship was demonstrated between ADHD symptoms and SDB (Hedges' g=0.57, 95% CI 0.36-0.78; P < 0.001). A high AHI cutoff was associated with lower effect sizes, while child age,

			Difference between ADHD symptomatology pre- versus post-adenotonsillectomy: 12 studies (529 subjects) were identified assessing pre- versus post-surgery ADHD symptoms	gender and BMI did not moderate the relationship between SDB and ADHD. Study quality was associated with larger effect sizes. *Difference between ADHD symptomatology pre- versus post-AT:* Hedges' g=0.43 (95% CI 0.30-0.55; P < 0.001) suggesting a medium effect i.e. adenotonsillectomy (for AHI ≥1 episode/h) was associated with decreased ADHD symptoms at 2-13 months postoperatively.
Amin et al, 2008 [109]	Prospective cohort study	III	140 participants: i) children (7-13 y.o.) with adenotonsillar hypertrophy, nightly snoring and AHI ≥1 episode/h; ii) age- and gender-matched healthy controls	24-hour ambulatory blood pressure monitoring revealed that children with obstructive AHI >5 episodes/h have an approximate mean increase of 3.5 mmHg in average wake systolic and wake and sleep diastolic blood pressure compared to healthy controls without snoring and with AHI ≤1 episode/h.
g. *Polysomnography vs. polygraphy*				
Author, year	**Type of Study**	**Class**	**Subjects**	**Methods and findings**
Certal et al, 2015 [211]	Systematic review and meta-analysis	-	Ten diagnostic studies with 724 patients were included in the systematic review, which was followed by a meta-analysis of 4 studies.	The analysis of two studies (76 patients) revealed a moderate sensitivity of 76%, a moderate specificity of 76% and a pooled diagnostic odds ratio of 15.18 (95% CI: 3.52–65.43). Using a cutoff of AHI >1 for the diagnosis of OSAS and based on the analysis of two studies (37 patients), the sensitivity was 88% and the specificity 71%.
h. *Primary snoring vs. upper airway resistance syndrome*				
Author, year	**Type of Study**	**Class**	**Subjects**	**Methods and findings**
Li et al, 2009 [111]	Cross-sectional, community-based study	IV	190 children (6-13 y.o.); 56 nonsnoring controls, 46 children with primary snoring, 62 children with AHI 1-3 episodes/h, and 26 children with an AHI > 3 episodes/h	Nocturnal sleep study and ambulatory blood pressure monitoring. Nocturnal diastolic blood pressure was significantly higher in children with primary snoring compared to controls after adjustment for age, gender, and body mass index.
Biggs et al, 2014 [212]	Review	-	13 studies with primary snoring confirmed by polysomnography.	Children with primary snoring have similar cognitive deficits and behavioral abnormalities to those in children with OSAS.

Question 4.3. What is the value of assessing obstructive SDB severity objectively?				
a. *Severity of obstructive SDB is positively associated with risk of morbidity*				
Author, year	**Type of Study**	**Class**	**Subjects**	**Methods and findings**
Alexopoulos et al, 2014 [165]	Hospital-based, retrospective cohort study	IV	525 children (≥ 5 y.o.; 7.5 ± 2.2 y.o.) with snoring who were referred for polysomnography over 12 years were reviewed.	Median obstructive AHI (10^{th}-90^{th} percentiles) was 1.9 (0.4-7.3) episodes/h. Three hundred and fifty five children (67.6%) had primary monosymptomatic nocturnal enuresis and 87 (16.6%) had moderate-to-severe OSAS. There was no interaction between enuresis and gender regarding the association with moderate-to-severe OSAS (P>0.05). Enuresis was associated significantly with presence of moderate-to-severe OSAS after adjustment for tonsillar hypertrophy, obesity, gender and age [adjusted OR = 1.92 (1.08-3.43); P=0.03]. Presence of nocturnal enuresis had high sensitivity (78.2%) and low positive predictive value (19.2%) for detecting moderate-to-severe OSAS and low specificity (34.5%) and high negative predictive value (88.8%) for ruling it out.
Chervin et al, 2014 [213]	Prospective cohort study	III	109 children with OSAS (AHI ≥1.5 episodes/h, mean 8.3 ± 10.6 episodes/h) and 24 children without OSAS (AHI 0.9 ± 0.3 episodes/h) who underwent adenotonsillectomy (ages 3-12 y.o.).	At baseline and again 7.2 ± 0.9 months later (approximately six months postoperatively), children underwent polysomnography, multiple sleep latency test, parent-completed behavioral rating scales, cognitive testing, and psychiatric evaluation. At baseline, the arousal index and the respiratory cycle-related EEG changes were not associated consistently with neurobehavioral comorbidities. At follow-up, the arousal index, the respiratory cycle-related EEG changes, and the neurobehavioral measures tended to improve. Improvement in arousals or the respiratory cycle-related EEG changes did not predict neurobehavioral outcomes postoperatively (P > 0.05).
Sedky et al, 2014 [131]	Meta-analysis	-	*Relationship between SDB and attention-deficit, hyperactivity disorder symptomatology:* 18 studies with 1113 children in the clinical group (874 had SDB and were examined for attention-deficit, hyperactivity disorder symptoms; 239	*Relationship between SDB and attention-deficit, hyperacivity disorder symptomatology:* Medium relationship was demonstrated between attention-deficit, hyperactivity disorder symptoms and SDB (Hedges' g=0.57, 95% CI 0.36-0.78; p< 0.001). A high AHI cutoff was associated

			had attention-deficit, hyperactivity disorder and were examined for SDB) and 1405 in the control-group. *Difference between attention-deficit, hyperactivity disorder symptomatology pre- versus post-adenotonsillectomy:* 12 studies (529 subjects) were identified assessing pre- versus post-surgery attention-deficit hyperactivity disorder symptoms	with lower effect sizes, while child age, gender and BMI did not moderate the relationship between SDB and attention-deficit, hyperactivity disorder. Study quality was associated with larger effect sizes. *Difference between ADHD symptomatology* *pre- versus post-AT:* Hedges' g=0.43 (95% CI 0.30-0.55; $p < 0.001$) suggesting a medium effect i.e. adenotonsillectomy (for AHI ≥1 episode/h) was associated with decreased ADHD symptoms at 2-13 months postoperatively.
Amin et al, 2008 [109]	Prospective cohort study	III	140 participants: i) children (7-13 y.o.) with adenotonsillar hypertrophy, nightly snoring and AHI ≥1 episode/h; ii) age- and gender-matched healthy controls	24-hour ambulatory blood pressure monitoring revealed that children with obstructive AHI >5 episodes/h have an approximate mean increase of 3.5 mmHg in average wake systolic and wake and sleep diastolic blood pressure compared to healthy controls without snoring and with AHI ≤1 episode/h.
Owens et al, 2008 [160]	Retrospective, cohort study	IV	235 children (3-18 y.o.) undergoing overnight polysomnography for symptoms of SDB	History of behavioral, emotional, and academic problems and Child Behavior Checklist (CBCL) scores were identified. 56% of subjects were overweight or at risk for overweight, 36% were short sleepers, and 49% had at least 1 additional sleep diagnosis. 47% had history of behavioral problems and 23% had reported diagnosis of attention-deficit/hyperactivity disorder. There were no significant differences in CBCL scores based on SDB severity. Increased weight was associated with increased internalizing CBCL scores ($P = 0.003$); short sleepers were more likely to have elevated externalizing scores ($P < 0.001$). The strongest predictor of adverse behavioral outcomes was the presence of at least 1 additional sleep diagnosis ($P < 0.001$).
Melendres et al, 2004 [124]	Prospective cohort study	IV	108 patients with suspected SDB (7 ± 4 y.o.) and 72 control subjects (8 ± 4 y.o.)	Polysomnography was performed in patients with suspected SDB. Patients with suspected SDB had higher modified Epworth Sleepiness Scale (ESS) (8.1 ± 4.9 vs 5.3 ± 3.9) and higher Conners Abbreviated Symptom Questionnaire score (12.8 ± 7.6 vs 9.0 ±

				6.2) than control subjects. There was no difference in the ESS and Conners scores of patients with primary snoring and patients with OSAS. The ESS had weak correlations with polysomnographic parameters.
b. *Moderate-to-severe OSAS is less likely to resolve without treatment when compared to mild OSAS*				
Author, year	**Type of Study**	**Class**	**Subjects**	**Methods and findings**
Marcus et al, 2013 [192]	Randomized controlled multicenter trial early adenotonsillectomy versus watchful waiting	I	464 (5-9 y.o.), 46% children in the watchful waiting group and 48% in the early treatment group were overweight or obese. Polysomnographic, cognitive, behavioral, and health outcomes were evaluated at baseline and at 7 months.	The two groups did not differ regarding change in the Developmental Neuropsychological Assessment from baseline to follow-up (P=0.16). There were significantly greater improvements in behavioral, quality-of-life, and polysomnographic outcomes and greater symptom reduction in the early-adenotonsillectomy group compared to the watchful-waiting group. Normalization of polysomnographic findings was observed in a larger proportion of children in the early-adenotonsillectomy group than in the watchful-waiting group (79% vs. 46%). In the watchful-waiting group, spontaneous OSAS resolution was more common in nonblack children (P <0.01), nonobese children (P <0.001), and children with a baseline AHI ≥4.7 episodes/h (P <0.001).
c. *OSAS severity predicts respiratory complications in the immediate post-adenotonsillectomy period*				
Author, year	**Type of Study**	**Class**	**Subjects**	**Methods and findings**
Konstantinopoulou et al, 2015 [214]	Multicenter, single-blind, randomized, controlled trial	I	464 children (5-9 y.o.) with OSAS and without comorbidities except for obesity or asthma were randomly assigned to early adenotonsillectomy (median baseline obstructive AHI 4.8 episodes/h) or watchful waiting (median baseline obstructive AHI 4.5 episodes/h). OSAS was defined as an obstructive AHI ≥2 episodes/h or an obstructive apnea index ≥1 episode/h.	Data from 221 children who underwent adenotonsillectomy were analysed. Associations between demographic variables and surgical complications were explored. Subjects with and without postadenotonsillectomy complications were compared regarding polysomnography variables. Preoperative AHI was 2-30 episodes/h and obstructive apnea index was 1.2-27.7 episodes/h and 31% of children were obese. 16 (7%) children had postoperative complications. 3 (1.4%) children had respiratory complications (pulmonary edema, hypoxemia and bronchospasm); 13 patients (5.9%) had non-respiratory complications (dehydration-4.5%; hemorrhage-2.3%; and fever-0.5%). There were no significant associations between gender,

				race, and obesity or polysomnographic parameters (AHI, % total sleep time with SpO_2<92%, SpO_2 nadir, % sleep time with end-tidal CO_2>50 mmHg) and presence of complications.
Horwood et al, 2014 [215]	Retrospective, cohort study	IV	362 children (median age 4.8 years; interquartile range 3.3-6.7 years; 61% male) with adenotonsillar hypertrophy and suspected OSAS who underwent pulse oximetry with analysis based on the McGill oximetry score.	Two-hundred-sixty-six (73%) had inconclusive oximetry and 96 (27%) had abnormal oximetry. 30% of children with inconclusive oximetry and 83% of those with abnormal oximetry underwent adenotonsillectomy. No child with an inconclusive oximetry required hospitalization for more than 1 night postoperatively whereas 14% of patients with an abnormal oximetry required hospitalization for 2 or 3 nights (P = 0.001). Frequencies of readmissions and emergency department visits were low regardless of inconclusive or abnormal oximetry results.
Jaryszak et al, 2011 [216]	Retrospective cohort study	III	1131 patients undergoing adenotonsillectomy; 151 patients (13.4%) underwent preoperative polysomnography	23 patients (15.2%) had adverse respiratory events. The primary adverse event was desaturation requiring supplemental oxygen therapy, with 1 case of post-obstructive pulmonary edema. Patients with adverse events had a significantly higher AHI (31.8 vs 14.1 episodes/h; P = 0.001), higher body mass index (z score, 1.43 vs 0.70; P = 0.02), and lower nadir SpO_2 (72% vs 84%; P <0.001). Patients with adverse events had a prolonged hospital course (OR 32.1; 95% CI 7.8-131.4).
Ye et al, 2009 [217]	Retrospective, cohort study	IV	475 consecutive cases for adenotonsillectomy were identified, and 321 children (4-14 y.o.) were included (AHI ≥5 episodes/h).	Demographic data, history, preoperative sleep evaluation, surgical and anesthetic management, and need for postoperative respiratory interventions were reviewed. 36 children (11.2%) had postoperative respiratory complications requiring an intervention. Of the 36, 29 children (80.6%) required an oropharyngeal or nasopharyngeal airway. Twenty-five children (69.4%) experienced multiple episodes of desaturation, and 61.1% of cases had respiratory complications in the postanesthesia care unit. Young age, obesity, and high preoperative AHI. An AHI of 26 had 74% sensitivity and 92% specificity for predicting postoperative respiratory

				complications.
Nixon et al, 2004 [218]	Prospective cohort study Phase 1: Development of oximetry score Phase 2: Retrospective validation of the score Phase 3: Prospective evaluation of the score	II	Phase 3: 230 children (median age 4.3 years) underwent nocturnal oximetry at home for suspected OSAS.	113 children underwent adenotonsillectomy and information on the postoperative course was available for 109 subjects. Oximetry was positive (at least 3 drops in SpO_2 to less than 90% and at least 3 clusters of desaturation (≤ 4%) events) in 22% of cases and detected 25 of 35 (sensitivity 71%) of those who required any intervention for postoperative respiratory compromise and 6 of 7 (sensitivity 86%) of those who had major postoperative respiratory compromise.
Wilson et al, 2002 [219]	Retrospective cohort study	IV	163	A preoperative AHI >5 episodes/h increased the risk for postopartive respiratory complications (OR 7.2; 95% CI 2.7-19.3). 34 children (21%) had postoperative respiratory complications requiring a medical intervention. Children with respiratory complications were younger (aged < 2 yr; adjusted OR 4.3; 95% CI 1.7-11) and had an associated medical condition (OR 3; 95% CI 1.4-6.5). A preoperative obstructive AHI ≥ 5 episodes/h increased the chance of postoperative respiratory complications (OR 7.2; 95% CI 2.7-19.3); also a preoperative oxygen saturation nadir ≤ 80% (OR 6.4; 95% CI 2.8-14.5).
d. *Likelihood of residual OSAS after adenotonsillectomy increases in parallel with preoperative disease severity*				
Author, year	**Type of Study**	**Class**	**Subjects**	**Methods and findings**
Marcus et al, 2013 [192]	Randomized controlled multicenter trial early adenotonsillectomy versus watchful waiting	I	464 (5-9 y.o.), 46% children in the watchful waiting group and 48% in the early treatment group were overweight or obese	33% of obese and 15% of nonobese children in the early adenotonsillectomy group vs. 71% of obese and 46% of nonobese in the watchful waiting group had residual OSAS (AHI >2 episodes/h or obstructive apnea index > 1 episode/h) at 7 months follow-up. Children with preoperative AHI >4.7 episodes/h were significantly more likely to have residual OSAS than subjects with lower preoperative AHI.
Bhattacharjee et al, 2010 [220]	Retrospective, multicenter study	IV	578 (mean age, 6.9 ± 3.8 years), 50.6% of subjects were obese	Age and body mass index z-score were the two principal predictors of

				postoperative AHI. Presence of asthma and magnitude of preoperative AHI were less important predictors among nonobese children.

Question 4.4. What are the alternative tools for the diagnosis of obstructive SDB if polysomnography or polygraphy are not available?				
a. *Ambulatory polysomnography or polygraphy*				
Author, year	**Type of Study**	**Class**	**Subjects**	**Methods and findings**
Alonso-Alvarez et al, 2015 [221]	Prospective, cohort study	II	27 boys and 23 girls (mean age 5.3 ± 2.5 years) with clinical suspicion of OSAS.	Initially home respiratory polygraphy was performed followed by in-laboratory overnight respiratory polygraphy and polysomnography. The AHI for home respiratory polygraphy was compared with the AHI for in-laboratory polysomnography; 66% of children were diagnosed with OSAS (obstructive respiratory disturbance index ≥3 episodes/h in the in-laboratory polysomnography). The optimal AHI for home respiratory polygraphy corresponding to the polysomnography-defined criterion for OSAS was ≥5.6 episodes//h Compared to in-laboratory polysomnography, home respiratory polygraphy had a sensitivity of 90.9% (95% CI, 79.6%-100%) and a specificity of 94.1% (95% CI, 80%-100%) for diagnosing OSAS.
Marcus et al, 2014 [222]	Cross-sectional	IV	201 children aged 5-12 years with history of premature birth who underwent unattended ambulatory polysomnography.	The initial rate of technically satisfactory polysomnography was 183 out of 201 (91%) children; 14 studies were repeated and ultimately the rate of satisfactory studies was 98%. Artifact-free signals were obtained for ≥75% of recording time in >92% of subjects; nasal pressure recording was satisfactory for ≥75% of recording time in 67% of children. The thermistor signal was satisfactory for ≥75% of recording time in 92% of subjects, and some measure of airflow in 96% of subjects. Mean total sleep time was 534 ± 73 minutes and sleep efficiency 92% ± 5%). Parental and children's rate of satisfaction was high.
Moss et al, 2005 [223]	Cross-sectional study	IV	50 children (mean age 10.1 years) recruited from a population sample.	Participants had polygraphy at home (chest and abdominal wall movements

				by piezo effort sensor, nasal pressure and nasal airflow, oral airflow by thermocouple, snoring by vibration sensor, pulse oximetry, actigraphy and body position). Recordings were technically successful in 89% of studies.
Poels et al, 2003 [224]	Cross-sectional study	IV	24 of 53 children (mean age 4.2 ± 1.6 years) who underwent adenotonsillectomy for snoring and/or apnea.	Participants underwent unattended cardiorespiratory monitoring at home; 75% of the recordings were technically acceptable and 29% of the studies were considered successful. The recording from the nasal cannula was often of poor quality.
Rosen et al, 2003 [99]	Prospective, cohort study	II	850 children (8-11 y.o.) were studied to define the frequency of undiagnosed SDB.	Participants had overnight in-home cardiorespiratory recordings of airflow, respiratory effort, oximetry, and electrocardiography. 94% of studies had technically satisfactory recordings for ≥ 4 h. In a subset of the subgroup, ambulatory recordings were compared to in-laboratory polysomnography; ambulatory studies had a sensitivity of 88% and specificity of 98% in detecting a laboratory-based AHI >5 episodes/h.
Zucconi et al, 2003 [225]	Prospective, cohort study	III	12 children (3-6 y.o.) suspected clinically uncomplicated OSAS	Participants had polysomnography and unattended cardiorespiratory monitoring in the sleep laboratory during 2 consecutive nights. 75% of children had respiratory disturbance index >5 episodes/h and 41.7% had a respiratory disturbance index >10 episodes/h in polysomnography. Sensitivity of the cardiorespiratory monitoring to detect a respiratory disturbance index >10 episodes/h was 100% and to identify an index >5 episodes/h was 89%. Specificity was 57% and 0%, respectively. Cardiorespiratory monitoring underestimated the frequency of obstructive hypopneas and overestimated the number of central apneas.
Goodwin et al, 2001 [226]	Cross-sectional study	IV	157 children recruited in the TuCASA study (5-12 years old; 43% female). .	Participants underwent polysomnography at home; nine children had a second study due to inadequate initial recording; the overall

				rate of technically acceptable studies was 97%; ≥5 hours of interpretable respiratory, electroencephalographic, and oximetry signals were obtained in 97% of participants. The poorest signal quality was obtained from the chin electromyogram and from the combination thermister/nasal cannula. There was a high degree of night-to-night reproducibility of key polysomnographic parameters.
Jacob et al, 1995 [227]	Prospective, cohort study	III	21 children (2-12 y.o.) underwent both polygraphy at home and in-laboratory polysomnography; 62 children had only polygraphy at home.	Polygraphy at home included pulse oximetry, electrocardiogram, respiratory inductive plethysmography, and an 8-hour videotape recording. In the laboratory, standard nocturnal polysomnography including electroencephalography was performed. Duration of recordings, AHI, desaturation index, respiratory and spontaneous movement/arousal indices, and oxygen saturation during sleep were similar for home and laboratory studies.
b. *Nocturnal pulse oximetry*				
Author, year	**Type of Study**	**Class**	**Subjects**	**Methods and findings**
Coverstone et al, 2014 [228]	Retrospective, cohort study	IV	119 consecutive children with trisomy 21 (median age 6 years; range 3 months-21 years) who underwent polysomnography for suspected obstructive SDB.	A McGill oximetry score of 1-4 was calculated from the polysomnography oximetry recording by scorers blinded to the polysomnography result and each child's clinical course. Median AHI was 4.6 episodes/h (range 0-101.8 episodes/h), median obstructive AHI was 2.5 episodes/h (range 0-101.1 episodes/h) and median central apnoea index was 1.1 episodes/h (0-35.2 episodes/h). 50% of patients had obstructive AHI ≥2.5 episodes/h. 49.6% of children had a McGill Score of 1 (inconclusive); their median obstructive AHI was 1.0 episode/h (interquartile range 0.4-3.3 episodes/h). McGill score was 2 in 36.1% of patients; their median obstructive AHI was 4.5 episodes/h (interquartile range 1.3-8.8 episodes/h). In 14.3% of patients the McGill score was 3 or 4; the median AHI was 16.1 episodes/h (interquartile range 9.3-45.5 episodes/h). In 10% of patients had central apnoea index was ≥2.5 episodes/h although obstructive AHI was <2.5 episodes/h) and 41.2% of them

				had McGill score of 2.
Horwood et al, 2014 [215]	Retrospective, cohort study	IV	362 children (median age 4.8 years; interquartile range 3.3-6.7 years; 61% male) with adenotonsillar hypertrophy and suspected OSAS who underwent pulse oximetry with analysis based on the McGill oximetry score.	Two-hundred-sixty-six (73%) had inconclusive oximetry and 96 (27%) had abnormal oximetry. 30% of children with inconclusive oximetry and 83% of those with abnormal oximetry underwent adenotonsillectomy. No child with an inconclusive oximetry required hospitalization for more than 1 night postoperatively whereas 14% of patients with an abnormal oximetry required hospitalization for 2 or 3 nights (P = 0.001). Frequencies of readmissions and emergency department visits were low regardless of inconclusive or abnormal oximetry results.
Chang et al, 2013 [229]	Retrospective, cohort study	III	141 children (21 m.o.-12.8 y.o.) referred for suspected OSAS	Parents completed a symptom questionnaire (snoring, reported apnea during sleep, mouth breathing, restless sleep) and children underwent polysomnography. Desaturation index (lower than 3% drop from baseline) was compared to result of polysomnography. 55% of subjects had OSAS (AHI >5 episodes/h). Reported apnea had 95% specificity and 84% positive predictive value. Presence of mouth breathing (score=1), restless sleep (score=1), desaturation index (≤1 episode/h, score=0; >1 and ≤3 episodes/h, score=1; >3 episodes/h, score 2) were used to estimate a total score. A total score ≥ 3 had 60% sensitivity, 86% specificity and 84% positive predictive value in diagnosing OSAS (AHI > 5 episodes/h).
Lee et al, 2013 [230]	Retrospective cohort study	III	231 children (≥ 3 y.o.) who underwent adenotonsillectomy and had a McGill oximetry score of 1 on home nocturnal oximetry	None of the patients had a major postoperative respiratory complication requiring re-intubation or hospital admission. 2.16% of patients had minor respiratory complications.
Pavone et al, 2013 [231]	Prospective cohort study	III	148 children (1.2-11.8 y.o.) referred for suspected OSAS	Two consecutive home nocturnal oximetries were performed and showed excellent night-to-night consistency of the McGill oximetry score (positive for OSAS vs inconclusive and also consistency of hypoxemia severity).
Tsai et al, 2013 [232]	Retrospective cohort study	III	148 children (3-12 y.o.) with snoring and suspected OSAS	Children underwent polysomnography. OSAS (AHI ≥1 episode/h) was

				diagnosed in 87.8% of participants. Desaturation index (drop ≥4%) >2.05 episodes/h predicted OSAS with a positive predictive value of 98.1%. Mild OSAS was predicted with a sensitivity of 77.7% and specificity of 88.9%.
Velasko Suárez et al, 2013 [233]	Prospective cohort study	III	167 children (2-16 y.o.) with adenotonsillar hypertrophy and suspected OSAS	Children underwent polysomnography and the mean duration was approximately 5 hours. The pulse oximetry recording was analyzed and was considered positive for OSAS (AHI >1 episode/h) if there were at least 2 clusters of desaturation events and and at least 1 SpO_2 fall below 90%. Pulse oximetry had 86.6% sensitivity, 98.9% specificity, 98% positive predictive value and 90.1% negative predictive value for detecting OSAS (increased negative predictive value compared to the study by Brouillette et al (2000).
Korndewal et al, 2012 [234]	Cross-sectional study	IV	53 children (1-3 y.o.) without respiratory or neurologic disorders, adenotonsillar hypertrophy or genetic abnormalities.	Children underwent nocturnal oximetry. There was a significant positive association between BMI z-score and % sleep time with SpO_2<95%.
Scholle et al, 2011 [200]	Cross-sectional study	IV	209 healthy German children (1-18 y.o.)	One-night polysomnography was performed in 16 laboratories. Normative values of cardiorespiratory parameters were summarized. No obstructive and mixed apneas were identified Hypopneas and central apneas (≥20 sec) were infrequent. In addition, oxygen desaturations or arousals accompanying central apneas were rare.
Arrarte et al, 2007 [235]	Prospective cohort study	IV	27 patients (5.2 ± 1.8 y.o.) with suspected SDB and clinical indication for adenotonsillectomy	Nocturnal oximetry was performed before and after surgery. Oxygen desaturation (≥4%) index decreased from a median of 1.63 to 0.65 episodes/h.
Saito et al, 2007 [202]	Prospective cohort study	III	232 children (1.4-10 y.o.) with symptoms indicative of SDB and 25 healthy children as controls.	All children had nocturnal oximetry and 86 of them underwent adenotonsillectomy and follow-up oximetry.Mean oxygen desaturation index (≥3%-ODI3) in controls was 0.74 episodes/h and standard deviation 0.65. Also mean oxygen desaturation index (≥4%-ODI4) was 0.21 and standard deviation 0.29. Improvements in ODI3 and ODI4 after adenotonsillectomy

				correlated significantly with preoperative values. 95% of subjects with ODI3 ≥ 3.5 episodes/h and/or ODI4 ≥ 1.5 episodes/h had improvement in the respective indices > twice the standard deviation in controls.
Nixon et al, 2004 [218]	Study in 3 phases	III	Phase 1-prospective: 64 children who underwent adenoidectomy and/or tonsillectomy Phase 2-retrospective:349 children who underwent adenoidectomy and/or tonsillectomy Phase 3-prospective: 230 children who underwent adenoidectomy and/or tonsillectomy	In phase 1, 4 categories of the McGill oximetry score were defined according to the presence of ≥3 clusters of desaturation events and the of 3 or more SpO_2 drops to <90%, <85% or <80% (normal/inconclusive oximetry, mild OSAS, moderate OSA or severe OSAS. Phases 2 and 3: The McGill oximetry score correlated with OSAS severity and predicted the risk of postoperative respiratory complications.
Kirk et al, 2003 [236]	Prospective cohort of hospital-referred children	IV	57 children (4-18 y.o.) referred to a sleep clinic for suspected OSAS.	Each participant was monitored by a portable oximetry monitor at home for 2 nights and had both oximetry monitoring and polysomnography in hospital. Desaturation index (>3%) calculated from the oximetry monitor had high test-retest reliability. A desaturation index value >5 episodes/h had 66.7% sensitivity and 60% specificity for the detection of AHI >5 episodes/h.
Urschitz et al, 2003 [237]	Population-based, cross-sectional study	IV	90 children recruited from primary schools (mean age 9.3 ± 0.6 years), 58 of whom did not have any respiratory complaints.	Children underwent nocturnal pulse oximetry at home (motion-resistant technology). The 2.5th centile for SpO_2 nadir was 88%, for median SpO_2 97%, for total drops below 90% was 1 and for desaturation index (≥4%) was 2.4 episodes/h.
Brouillette et al, 2000 [238]	Cross-sectional study	III	349 children (6 m.o.-18 y.o.) who were referred for polysomnography due to suspected OSAS.	Children underwent polysomnography including nocturnal oximetry with a mean sleep time of 8.1 ± 1.4 hours. OSAS was defined as a mixed/obstructive apnea/hypopnea index ≥ 1 episode/h. Oximetry was considered positive for OSAS if there were 3 or more clusters of desaturations (≥5 desaturations ≥4% within 10-30 min) and ≥3 desaturations to <90%. Of the 93 oximetry recordings read as positive, polysomnography confirmed OSAS in 90 patients (97% positive predictive value). However, children

				with a negative or inconclusive oximetry had 47% probability of having OSAS.
c. *Pulse transit time*				
Author, year	**Type of Study**	**Class**	**Subjects**	**Methods and findings**
Bradley et al, 2012 [239]	Prospective, cohort study	IV	Selected sample at high risk of OSAS (n=51; mean age 11.2 years).	Simultaneous pulse transit time measurement and polysomnography. Pulse transit time arousal index > 11 episodes/ hour predicted AHI > 3 episodes/hour with 94% sensitivity and 62% specificity.
Brietzke et al, 2007 [240]	Prospective cohort study	III	Patients with suspected OSA and adenotonsillar hypertrophy, obesity or craniofacial abnormalities (n=59; mean age 7.8 years).	Subjects underwent monitoring of pulse transit time and overnight polysomnography simultaneously. Pulse transit time arousal index correlated significantly with AHI (r=0.70; P <0.001). Pulse transit time arousal index > 5.4 episodes/h had sensitivity of 81% and specificity of 76% for the prediction of OSAS (AHI ≥1 episode/h).
Katz et al, 2003 [241]	Prospective cohort study	III	Children (2-16 y.o.) suspected for SDB and healthy controls (n=5 with OSAS; n=14 with UARS; n=5 symptoms of OSAS; n = 10 control group-no snoring)	Children had monitoring of pulse transit time and polysomnography (some with esophageal manometry). Pulse transit time arousal index was elevated in children with OSA compared to children with primary snoring.
d. *OSAS score and OSA-18 quality-of-life questionnaire*				
Author, year	**Type of Study**	**Class**	**Subjects**	**Methods and findings**
Borgstrom et al, 2013 [242]	Cross-sectional study using an existing database	IV	225 children (1-12 y.o.) who had nocturnal polysomnography and their caregivers answered the OSA-18 quality-of-life questionnaire	A total score of the OSA-18 ≥ 60 had 55.2% sensitivity and 40.9% specificity to predict AHI >1 episode/h; for AHI ≥5 episodes/h the sensitivity was 59.3% and the specificity 48.4%. For the subscale of sleep disturbance, there was poor correlation with the AHI values.
Constantin et al, 2010 [243]	Cross-sectional study	IV	334 children (2-10 y.o.) suspected for OSAS who underwent nocturnal oximetry and the OSA-18 questionnaire was completed by their parents.	An OSA-18 score ≥ 60 had 40% sensitivity and 73% negative predictive value to predict a McGill oximetry score >1 i.e. moderate-to-severe OSAS.
Schechter et al, 2002 [244]	Clinical practice guideline-technical report; meta-analysis	-	765 children suspected for OSAS	Meta-analysis of four studies with an overall prevalence of OSAS of 60% as demonstrated by polysomnography. The OSAS score was indeterminate in 47% of children and had sensitivity of 59.5% and specificity of 51.9% for the diagnosis of OSAS (AHI ≥1 episode/h or apnea index ≥1 episode/h.

Brouillette et al, 1984 [245]	Prospective	III	92 children (phase I: 23 children with OSAS and 46 controls; phase II: 23 children with suspected OSAS)	A score, obtained on the basis of frequency of difficulty during sleep, apnea observed during sleep and snoring (phase I); during validation phase II, OSAS score >3.5 predicted the presence of OSAS by polysomnography; a score of <−1 predicted absence of OSAS; and a score in between was indeterminate.
e. *Pediatric sleep questionnaire*				
Author, year	**Type of Study**	**Class**	**Subjects**	**Methods and findings**
Rosen et al, 2015 [246]	Multicenter, single-blind, randomized, controlled trial	I	464 children (5-9 y.o.) with OSAS randomly assigned to early adenotonsillectomy (median baseline obstructive AHI 4.8 episodes/h) or watchful waiting (median baseline obstructive AHI 4.5 episodes/h). Baseline and 7-month follow-up data were analysed from 185 children in the early adenotonsillectomy arm. Associations were assessed between baseline Pediatric Sleep Questionnaire score or AHI and postoperative changes in the NEPSY and executive function, behavior, quality of life and sleepiness as rated by parents.	Higher baseline Pediatric Sleep Questionnaire scores-but not the baseline AHI- predicted postadenotonsillectomy improvement in executive functioning, behavior, quality of life, and sleepiness as rated by parents. Neither the Pediatric Sleep Questionnaire nor polysomnographic parameters were associated with objectively assessed executive dysfunction (NEPSY score) or its improvement postoperatively.
Chervin et al, 2007 [247]	Retrospective analysis of data from a longitudinal study.	II	105 children (The Washtenaw County Adenotonsillectomy Cohort) with ages 5-12.9 years at entry.	At baseline, a high sleep-related breathing disorder scale score (1 standard deviation above the mean) predicted increased risk of OSAS on polysomnography (odds ratio, 2.80; 95% confidence interval, 1.68-4.68). One year after adenotonsillectomy, OSAS and symptoms had resolved, but a high score predicted an increased risk of residual OSAS on polysomnography (odds ratio, 1.89; 95% confidence interval, 1.13-3.18). Compared with polysomnography, the baseline score better predicted initial hyperactivity ratings and improvement at 1 year, similarly predicted sleepiness and its improvement, and similarly failed to predict attention deficit and its improvement. Sensitivity for predicting OSAS as defined by polysomnography was 78% and specificity 72%.
Chervin et al, 2000 [248]	Cross-sectional study	IV	54 subjects (2-18 y.o.) with OSAS (AHI >5 episodes/h) or excessively negative esophageal pressure and 108 controls recruited at two general pediatrics	Parents completed a Pediatric Sleep Questionnaire which contained several items. Item reduction lead to a 22-item Sleep-Related Breathing Score that was

			clinics.	significantly associated with diagnosis of a sleep-related breathing disorder (P<0.0001). Sensitivity was 81-85% and specificity 87%.
f. *Sleep Clinical Record*				
Author, year	**Type of Study**	**Class**	**Subjects**	**Methods and findings**
Villa et al, 2013 [249]	Prospective study	IV	279 children (age 6.1 ± 3.1 years); 27.2% with primary snoring and 72.8% with OSAS.	The Sleep Clinical Record Score was higher in the OSA group compared to the primary snoring group (8.1 ± 9.6 versus 0.4 ± 0.3; P<0.005), correlated with the AHI (P=0.001) and had a sensitivity of 96.05% and specificity of 67% for the prediction of AHI >1 episode/h.

Online Supplementary Table 5.

Step 5: Determine indications for treatment of SDB

Question 5.1. In which cases and why obstructive SDB is usually treated?				
a. *AHI >5 episodes/h*				
Author, year	**Type of Study**	**Class**	**Subjects**	**Methods and findings**
Marcus et al, 2013 [192]	Multicenter, single-blind, randomized, controlled trial	I	464 children (5-9 y.o.) with OSAS randomly assigned to early adenotonsillectomy (median baseline obstructive AHI 4.8 episodes/h) or watchful waiting (median baseline obstructive AHI 4.5 episodes/h). OSAS was defined as an obstructive AHI ≥2 episodes/h or an obstructive apnea index ≥1 episode/h.	Polysomnographic, cognitive, behavioral, and health outcomes were assessed at baseline and at 7 months. Average baseline value for the attention and executive-function score on the Developmental Neuropsychological Assessment (primary outcome), was close to the population mean of 100, and the change from baseline to follow-up did not differ significantly between the early-adenotonsillectomy group and the watchful-waiting group; P=0.16). There were significantly greater improvements in behavioral, quality-of-life, and polysomnographic findings and significantly greater reduction in symptoms in the early-adenotonsillectomy group compared to the watchful-waiting group. Normalization of polysomnographic findings was observed in a larger proportion of children in the early-adenotonsillectomy group than in the watchful-waiting group (79% vs. 46%). Among children who underwent early adenotonsillectomy, the frequency of normalized AHI was significantly higher among children

				who were not black (P<0.001), children who were not obese (P<0.001), and children who had a baseline AHI ≤4.7 episodes/h (86%) (P<0.05). Among children assigned to watchful waiting, the frequency of normalized polysomnography at follow-up was significantly higher among nonblack children (P<0.05), nonobese children (P<0.001), and children with a baseline AHI ≤4.7 episodes/h (65%) (P<0.001).
Friedman et al, 2009 [250]	Updated systematic review and meta-analysis	-	23 studies including 1079 subjects with age <20 years (mean sample size/study=42 with range of 10 to 199). Obese patients were not excluded. Complicated children were considered those with morbid obesity, severe OSAS or age <3-5 years.	The mean preoperative AHI in each study varied from 6.9 episodes/h to 69.3 episodes/h. The random-effects model estimate for treatment success (defined as AHI<1) after adenotonsillectomy was 59.8 % (95% CI 43.6%-74.0%; P=0.234). Cure rate was 73.8% in uncomplicated patients i.e. significantly higher than the cure rate of 38.7% in complicated patients (P<0.0001).
Brietzke et al, 2006 [251]	Meta-analysis	-	355 children in 14 studies (mean sample size/study =28); mean age 4.4-7.5 years	The mean preoperative AHI in each study varied from 6.375 episodes/h to 31.5 episodes/h. Random-effects model esimate for treatment success with adenotonsillectomy was 82.9 % (95% CI 76.2-89.5%; p< 0.001) (success criterion varied per individual article).
b. *AHI 1-5 episodes/h and i) morbidity from the cardiovascular system; ii) morbidity from the central nervous system; iii) somatic growth delay or growth failure; iv) enuresis; v) decreased quality of life or vi) risk factors for persistence of OSAS*				
Author, year	**Type of Study**	**Class**	**Subjects**	**Methods and findings**
Kheirandish-Gozal et al, 2014 [252]	Retrospective cohort study	IV	3,071 children (2-14 y.o.) were diagnosed with OSAS; in 836 of them OSAS was of mild severity.	Children with OSAS and obstructive AHI > 5 episodes/h were referred for adenotonsillectomy or CPAP, while those with obstructive AHI >1 and <5 episodes/h were recommended treatment with an intranasal corticosteroid and oral montelukast for at least 12 weeks, following which a second overnight sleep study was performed to evaluate efficacy; 752 children received montelukast and intranasal corticosteroid; 445 patients underwent follow-up polysomnography; 62% of children with mild OSAS treated with a combination of oral for 12 weeks had normal sleep studies at the end of the 12 weeks period (obstructive AHI <1

				episode/h). Older and obese children were significantly more likely to be non-responders (OR: 2.3; 95% CI: 1.43-4.13; P<0.001 and OR: 6.3; 95% CI: 4.23-11.18; P<0.000001, respectively).
i) cardiovascular morbidity				
Quante et al, 2014 [106]	Multicentre, single-blind, randomised, controlled trial	I	464 children (5-9 y.o.) with OSAS randomly assigned to early adenotonsillectomy (median baseline obstructive AHI 4.8 episodes/h) or watchful waiting (median baseline obstructive AHI 4.5 episodes/h). OSAS was defined as an obstructive AHI ≥2 episodes/h or an obstructive apnea index ≥1 episode/h.	There was a positive association between nocturnal heart rate and baseline OSAS severity (average heart rate increase of 3 beats per minute for AHI of 2 versus 10 episodes/h. For each 5-unit improvement in AHI and 5 mmHg improvement in peak end-tidal CO2 there was a reduction in heart rate by 1 and 1.5 beats per minute, respectively.
Weber et al, 2014 [253]	Systematic review and meta-analysis	-	7 cohort studies including children ≤12 y.o. who were diagnosed with OSAS by polysomnography and/or clinical evaluation and underwent surgery for adenotonsillar hypertrophy and subjects without OSAS ≤12 y.o. as comparison group. Studies had 55-110 participants; none of them had history of neuromuscular disorders or craniofacial abnormalities.	A significantly higher mean pulmonary arterial pressure was demonstrated in children with OSAS than in those without OSAS (mean difference 8.67; 95% confidence interval 6.09-11.25). Participants with OSAS had significantly increased interventricular septum thickness and right ventricular dimension.
Martha et al, 2013 [254]	Prospective, cohort study	IV	33 children (1-12 y.o.) with adenotonsillar hypertrophy and snoring or oral breathing without genetic syndromes, neuromuscular disorders or craniofacial abnormalities; 10 healthy control chidlren.	Participants underwent echocardiography before and after adenoidectomy or adenotonsillectomy. Pulmonary hypertension (mean pulmonary artery pressure ≥25 mmHg) in a group of children with, and to verify the pulmonary arterial pressure changes after surgery. Pulmonary hypertension was identified in 12 (36%) of the 33 children with adenotonsillar hypertrophy. In children with pulmonary arterial hypertension, adenoidectomy or adenotonsillectomy were accompanied by a significant decrease in mean pulmonary arterial pressure (from 27 ± 2.8 to 20 ± 5.1 mmHg; P<0.001) and by a non-significant decrease in systolic pulmonary arterial pressure (from 35 ± 6.2 mmHg to 25 ± 0.5 mmHg, P=0.243). The pulmonary arterial values in children without pulmonary hypertension did not change postoeratively.

Teo et al, 2013 [255]	Systematic review	-	14 studies evaluating the effects of adenotonsillectomy on cardiovascular parameters in children with OSAS were summarized. In 10 studies OSAS was defined based on clinical criteria and in 4 studies polysomnography was carried out. Publications included case-control studies, cohort studies without control subjects, case series or case reports (n=418; age range 2-10 years mean baseline AHI 9.2-14 episodes/h).	3 studies evaluated changes in blood pressure, 7 studies assessed changes in cardiac structure and function, 6 studies explored changes in pulmonary artery pressure and 1 study assessed changes in heart rate variability. Published reports were of low methodological quality. Overall, cardiovascular parameters improved following adenotonsillectomy.
Vlahandonis et al, 2013 [256]	Systematic review	-	The following studies including changes of cardiovascular parameters following treatment for SDB were reviewed: 4 studies on hypoxemia; 3 studies on blood pressure; 4 studies on cardiovascular control; 8 studies on onflammation and endothelial function; 3 studies on cardiac structure and function	No consistent changes in blood pressure were identified following adenotonsillectomy. There was improvement in both left and right ventricular function.
ii) central nervous system morbidity				
Garetz et al, 2015 [173]	Multicentre, single-blind, randomised, controlled trial	I	464 children (5-9 y.o.) with OSAS randomly assigned to early adenotonsillectomy (median baseline obstructive AHI 4.8 episodes/h) or watchful waiting (median baseline obstructive AHI 4.5 episodes/h). OSAS was defined as an obstructive AHI ≥2 episodes/h or an obstructive apnea index ≥1 episode/h. The Pediatric Quality of Life inventory, the Sleep-Related Breathing Scale of the Pediatric Sleep Questionnaire, the 18-item Obstructive Sleep Apnoea QoL instrument, and the modified Epworth Sleepiness Scale were completed before adenotonsillectomy and at 7 months postoperatively.	Greater improvements regarding most measures of quality of life and symptom severity were demonstrated in the early adenotonsillectomy group than in the watchful waiting arm. There was weak correlation between improvement in polysomnography indices and changes in quality of life or symptom severity measures. Baseline OSAS severity did not influence the association between quality of life or symptom severity measures and treatment arm.
Rosen et al, 2015 [246]	Multicenter, single-blind, randomized, controlled trial	I	464 children (5-9 y.o.) with OSAS randomly assigned to early adenotonsillectomy (median baseline obstructive AHI 4.8 episodes/h) or watchful waiting (median baseline obstructive AHI 4.5 episodes/h). Baseline and 7-month follow-up data were analysed from 185 children in the early adenotonsillectomy arm. Associations were assessed between baseline Pediatric Sleep Questionnaire score or AHI and postoperative changes	Higher baseline Pediatric Sleep Questionnaire scores-but not the baseline AHI- predicted postadenotonsillectomy improvement in executive functioning, behavior, quality of life, and sleepiness as rated by parents. Neither the Pediatric Sleep Questionnaire nor polysomnographic parameters were associated with objectively assessed executive dysfunction (NEPSY score) or its improvement postoperatively.

			in the NEPSY and executive function, behavior, quality of life and sleepiness as rated by parents.	
Sedky et al, 2014 [131]	Meta-analysis	-	*Relationship between SDB and attention-deficit, hyperactivity disorder symptomatology:* 18 studies with 1113 children and mean age 8.37 years in the clinical group (874 had SDB and were examined for attention-deficit, hyperactivity disorder symptoms; 239 had attention-deficit, hyperactivity disorder and were examined for SDB) and 1405 in the control group with mean age 8.54 years. *Difference between attention-deficit, hyperactivity disorder symptomatology pre- versus post-adenotonsillectomy:* 12 studies (529 subjects) were identified assessing pre- versus post-surgery attention-deficit, hyperactivity disorder symptoms	*Relationship between SDB and attention-deficit, hyperactivity symptomatology:* Medium relationship was demonstrated between attention-deficit, hyperactivity symptoms and SDB (Hedges' g=0.57, 95% CI 0.36-0.78; p< 0.001). A high AHI cutoff (>4-5 episodes/h) was associated with lower effect sizes, while child age, gender and BMI did not moderate the relationship between SDB and attention-deficit, hyperactivity disorder. Better study quality was associated with larger effect sizes. *Difference between attention-deficit, hyperactivity disorder symptomatology pre- versus post-AT:* Hedges' g=0.43 (95% CI 0.30-0.55; p < 0.001) suggesting a medium effect i.e. adenotonsillectomy was associated with decreased attention-deficit, hyperactivity disorder symptoms at 2-13 months postoperatively.
Marcus et al, 2013 [192]	Multicentre, single-blind, randomised, controlled trial	I	464 children (5-9 y.o.) with OSAS randomly assigned to early adenotonsillectomy (median baseline obstructive AHI 4.8 episodes/h) or watchful waiting (median baseline obstructive AHI 4.5 episodes/h). OSAS was defined as an obstructive AHI ≥2 episodes/h or an obstructive apnea index ≥1 episode/h.	Polysomnographic, cognitive, behavioral, and health outcomes were assessed at baseline and at 7 months. Average baseline value for the attention and executive-function score on the Developmental Neuropsychological Assessment (primary outcome), was close to the population mean of 100, and the change from baseline to follow-up did not differ significantly between the early-adenotonsillectomy group and the watchful-waiting group; P=0.16). There were significantly greater improvements in behavioral, quality-of-life, and polysomnographic findings and significantly greater reduction in symptoms in the early-adenotonsillectomy group compared to the watchful-waiting group. Normalization of polysomnographic findings was observed in a larger proportion of children in the early-adenotonsillectomy group than in the

				watchful-waiting group (79% vs. 46%).
Giordani et al, 2012 [257]	Prospective cohort study	II	78 children (5-12 y.o.) mostly with symptoms of SDB (in 90% of cases) who underwent adenotonsillectomy (n=40 wih OSAS and n=38 without OSAS); controls (n=27) of similar age range	At 1 year after adenotonsillectomy there were improvements in polysomnography, sleepiness and parental reports of behavior, with mixed changes in cognitive outcomes. Children undergoing adenotonsillectomy with and without polysomnography-confirmed OSAS improved in academic achievement measures, short-term attention/working memory, executive functioning, and parental ratings of behavior. Measures of verbal abstraction ability, arithmetic calculations, visual and verbal learning, verbal delayed recall, sustained attention demonstrated declines. The performance of the control group over the same observation period was used to address developmental and retest issues. It was not confirmed that adenotonsillectomy is accompanied by resolution of all or at least most behavioral and cognitive difficulties in children with SDB.
Kohler et al, 2010 [258]	Systematic review	-	Only studies with SDB diagnosed by polysomnography were included (published till November 2009): 27 adenotonsillectomy studies; 2 tracheostomy studies; 1 study with unspecified surgery and continuous positive airway pressure	Neurocognitive and behavioral outcomes were assessed before and after treatmernt for SDB. Most studies were focused on children of school age and the follow-up data period was less than a year. In many studies, no postoperative polysomnography was performed and control subjects were not evaluated at two time points. Overall, improvement was demonstrated in global intelligence, attention, and visual–spatial ability, but deficits in language and short-term memory appear to persist. Hyperactivity, aggression and conduct problems and somatic complaints also improved postoperatively. However, symptoms of anxiety and social problems did not seem to change.
Garetz et al, 2008 [259]	Systematic review	-	25 articles with sample sizes of 19 to 297 subjects with SDB who underwent adenotonsillectomy; 10 studies evaluated postoperative changes in quality of life, 4 studies changes in behavior, and 3 studies changes in	All studies demonstrated improvements in one or more of the following domains: quality of life, behavioral problems (including hyperactivity and aggression), and neurocognitive skills (memory, attention, or school performance). There was poor

			neurocognitive skills; 5 studies evaluated improvement in behavior and cognition, and 2 studies examined improvement in behavior and quality of life; 1 study evaluated changes in cognition, behavior, and quality of life. No randomized controlled trials were identified.	correlation between improvements in outcome measures and polysomnographic variables.
Chervin et al, 2006 [260]	Prospective cohort study	II	105 children (5-12.9 y.o.): 78 scheduled for clinically indicated adenotonsillectomy, usually for SDB (in 91% of cases), and 27 for unrelated surgical care (controls)	Subjects undergoing adenotonsillectomy for suspected SDB (mean AHI 7,3 episodes/h), as compared to controls (mean AHI 1,2 episodes/h), were more hyperactive on parent rating scales, inattentive on cognitive testing, more sleepy on the Multiple Sleep Latency Test, and more likely to have attention-deficit/hyperactivity disorder as judged by a child psychiatrist. At 1 year follow-up, the 2 groups showed no significant differences in the same measures. Subjects who underwent adenotonsillectomy improved in all measures, and control subjects improved in none. Polysomnographic indices at baseline and at follow-up did not predict baseline neurobehavioral morbidity or improvement in any area other than sleepiness.
iii) enuresis				
Kovacevic et al, 2014 [261]	Prospective, cohort study	IV	46 children (5-18 y.o.) with snoring or OSAS and monosymptomatic primary nocturnal enuresis who underwent adenotonsillectomy as treatment for upper airway obstruction	Polysomnography revealed OSAS in 71.7% of patients and snoring in 28.3%. Plasma antidiuretic hormone and brain natriuretic peptide were measured preoperatively and 1 month postoperatively in 32 children. The mean number of wet nights weekly before surgery was 6.39 ± 1.26. After adenotonsillectomy 43.5% of patients became dry. Children who became dry had significantly more arousals and obstructive apnea episodes but fewer awakenings before adenotonsillectomy than children who remained wet. Significant increases in plasma antidiuretic hormone and decreases in plasma brain natriuretic peptide levels were demonstrated in all children after adenotonsillectomy irrespective from resolution of enuresis.

Thottam et al, 2013 [262]	Prospective, cohort study	IV	37 children (mean age 8 ± 2.32 years) with primary nocturnal enuresis who underwent adenotonsillectomy for OSAS	Children with and without resolution of enuresis after adenotonsillectomy did not differ in age or gender. Postoperatively, enuresis resolved in more than 50% of cases. More boys than girls had persistence of enuresis (P=0.06). Nocturnal enuresis improved in children with a higher obstructive AHI (>10 episodes/h) and more episodes of desaturation. 11 of 12 children with prolonged stage 2 sleep had resolution of enuresis (P = 0.001). Logistic regression analysis demonstrated that an elevated body mass index and the interaction of severe OSAS and prolonged stage 2 sleep predicted resolution of nocturnal enuresis.
Jeyakumar et al, 2012 [164]	Systematic review	-	Pediatric studies from 1980 to 2010 on the association of SDB with enuresis and the effects of adenotonsillectomy were reviewed. 14 studies were reviewed including 3,550 children (age 18 months-19 years) with SDB, of whom one-third (n = 1,113) had a diagnosis of enuresis; in 7 studies (n =1,360) frequency of enuresis was evaluated also post-adenotonsillectomy (median follow-up of 6 months; age range of 2-18 years).	Preoperative prevalence of enuresis was 31% and postoperative prevalence was 16% (P <0.0002). Most studies did not separate primary from secondary enuresis. Some subjects probably had age-appropriate enuresis. One study including a control population showed no differences in enuresis cure rate between patients that underwent adenotonsillectomy (50%) and controls (48%) after 6 months of observation.
Waleed et al, 2011 [263]	Prospective, cohort study	IV	153 participants (5-10 y.o.) with primary nocturnal enuresis; 47 with enuresis and SDB; 106 with enuresis but without SDB	SDB was diagnosed with polysomnography or nocturnal oximetry. 33 of 47 children with SDB and enuresis underwent adenoidectomy and/or tonsillectomy. All enuretic children with SDB who underwent surgery had significant reduction in the prevalence of enuresis.
iv) somatic growth delay or growth failure				
Katz et al, 2014 [264]	Multicentre, single-blind, randomised, controlled trial	I	464 children (5-9 y.o.) with OSAS randomly assigned to early adenotonsillectomy (median baseline obstructive AHI 4.8 episodes/h) or watchful waiting (median baseline obstructive AHI 4.5 episodes/h) and were followed for 7 months. OSAS was defined as an obstructive AHI ≥2 episodes/h or an obstructive apnea index ≥1 episode/h.	Polysomnography and measurement of weight and height were performed at baseline and 7-month follow-up. Multivariable regression modeling was used to predict the change in weight and growth indices. During the observation period body mass index z-score increased in both arms, but it was greater in the early adenotonsillectomy (P < 0.0001). A greater proportion of overweight children in the early

				adenotonsillectomy group became obese during the 7-month observation period compared to participants in the watchful waiting group (52% vs. 21%; $P < 0.05$). Baseline AHI was positively associated with the postoperative body mass index z- score change.
Hsu et al, 2013 [171]	Retrospective, cohort study	IV	161 children (mean age, 7.0 ± 3.4 years; 78% boys) with OSAS who underwent adenotonsillectomy.	All patients had polysomnography before and after surgery. Children were classified into underweight, normal weight, overweight and obese, based on age and gender corrected body mass index. Postoperatively, all four groups significantly improved regarding AHI and SpO_2 nadir. 49.1% of all children (79/161) had residual OSAS (AHI ≥ 1 episode/h). The incidence of residual OSAS in the obese group was 75%, which was significantly higher compared to the other three groups ($P<0.01$). 54% (13/24) of the underweight children attained normal weight status within 6 months after surgery.
Bonuck et al, 2009 [172]	Systematic review and meta-analysis	-	20 cohort studies describing changes in weight, height, IGF-1 and/or IGFBP-3 serum-levels as z-scores, percentiles or raw data following adenotonsillectomy were reviewed. Studies ranged in numbers of participants from 14 to 204 children and ages of 5 months to 15.8 years with follow-up of 1 month to 3 years.	6 of 20 studies reported growth failure in a proportion of their participants. Results of meta-analysis regarding postoperative changes compared to preoperative values were reported. Standardised height (10 studies; n=363): pooled standardised mean differences (SMD) = 0.34 (95% CI 0.20-0.47); standardised weight (11 studies; n=390): pooled SMD = 0.57 (95% CI 0.44-0.70); IGF-1 (7 studies; n=177): pooled SMD = 0.53 (95% CI 0.33-0.73); IGFBP-3: (7 studies; n=177): pooled SMD = 0.59 (95% CI 0.34 to 0.83).
Amin et al, 2008 [265]	Prospective, cohort study	III	62 children with OSAS and adenotonsillar hypertrophy and 35 control participants (7-13 y.o.)	OSAS group had serial polysomnographies and BMI calculation before adenotonsillectomy and 6 weeks, 6 months, and 1 year postoperatively. Respective measurements were obtained for the control group. Children who were obese at baseline were at risk of increased weight gain postoperatively and recurrence of OSAS at 1 year after surgery.
v) decreased quality of life				

Garetz et al, 2015 [173]	Multicentre, single-blind, randomised, controlled trial	I	464 children (5-9 y.o.) with OSAS randomly assigned to early adenotonsillectomy (median baseline obstructive AHI 4.8 episodes/h) or watchful waiting (median baseline obstructive AHI 4.5 episodes/h). OSAS was defined as an obstructive AHI ≥2 episodes/h or an obstructive apnea index ≥1 episode/h. The Pediatric Quality of Life inventory, the Sleep-Related Breathing Scale of the Pediatric Sleep Questionnaire, the 18-item Obstructive Sleep Apnoea QoL instrument, and the modified Epworth Sleepiness Scale were completed before adenotonsillectomy and at 7 months postoperatively.	Greater improvements regarding most measures of quality of life and symptom severity were demonstrated in the early adenotonsillectomy group than in the watchful waiting arm. There was weak correlation between improvement in polysomnography indices and changes in quality of life or symptom severity measures. Baseline OSAS severity did not influence the association between quality of life or symptom severity measures and treatment arm.
Volsky et al, 2014 [266]	Prospective, cohort study	III	64 children (3-16 y.o.) with mild OSAS (AHI 1-5 episodes/h); 30 patients chose adenotonsillectomy, and 34 chose observation.	At baseline, early and late follow-up visits, caregivers completed two validated quality-of-life instruments (OSA-18 and Children's Health Questionnaire). At baseline, children in the adenotonsillectomy group had significantly poorer total OSA-18 scores than those in the observation group (72.3 vs. 58.5; P=0.01). At 4 months after surgery, OSA-18 scores improved by 39.1 points compared to baseline (P = 0.0001), but there was no change in the observation group (P >0.05). At 8 months postoperatively, OSA-18 scores remained improved in the surgery group but there was no statistically significant difference compared to the observation group (P=0.05).
Katyal et al, 2013 [267]	Prospective, cohort study	IV	81 children (age 8-17 years) recruited from an orthodontic clinic	Participants were classified as low risk or high risk for OSAS based on results of the OSA-18 questionnaire. All children underwent cephalometric assessment and dental cast analysis at baseline. 10 children who had rapid maxillary expansion were followed longitudinally until removal of the appliance (approximately 9 months). Frequency of palatal crossbite (at least 3 teeth) was significantly higher in the high-risk group than in the low-risk group at 68.2% vs. 23.2%; P <0.0001). Mean inferior airway space, posterior nasal spine to adenoidal mass distance, and adenoidal mass to soft palate

				distance were decreased in the high-risk group compared with the low-risk group (P<0.05). Also, the mean maxillary intercanine, maxillary interfirst premolar, maxillary interfirst molar, mandibular intercanine, and mandibular interfirst premolar widths were reduced in the high-risk group compared with the low-risk group (P<0.05). Children in the high-risk group who underwent rapid maxillary expansion had an average improvement of 14% in quality of life scores. In contrast, children in the low-risk group, there was a slight worsening in quality of life related to SDB by an average of 1% following rapid maxillary expansion.
Marcus et al, 2013 [192]	Multicenter, single-blind, randomized, controlled trial	I	464 children (5-9 y.o.) with OSAS randomly assigned to early adenotonsillectomy (median baseline obstructive AHI 4.8 episodes/h) or watchful waiting (median baseline obstructive AHI 4.5 episodes/h)	Quality of life (Pediatric Quality of Life Inventory, PedsQL and the OSA-18 score) and polysomnography were assessed at baseline and at 7 months. AHI normalized in significantly more children in the early-adenotonsillectomy group than in the watchful-waiting group (79% vs. 46%; P<0.05). The early-adenotonsillectomy group had significantly greater improvement in quality of life (PedsQL and OSA-18) than the watchful-waiting group.
Randhawa et al, 2011 [268]	Prospective, cohort study	III	4-year follow-up study of 33 children (mean age 10.6 years; median 11 years; range 5-16 years) who underwent adenotonsillectomy for OSAS (18 girls) and of 221 healthy controls (6-18 y.o.).	The Child Health Questionnaire Parental Form version-28 was completed 4 years after adenotonsillectomy. When compared to data at 3 months postoperatively, the mean scores were higher in five domains and statistically significant in three subscales (Role Limitations; P < 0.00001; Bodily Pain; P < 0.002; and Global Health P < 0.02). There was a significant deterioration in Behaviour subscale (P < 0.007). Compared with controls, at the 4-year follow-up, scores were higher in five domains with statistically significant difference in the Global Health domain (P < 0.0004). Improvements after adenotonsillectomy persisted 4 years postoperatively.
Baldassari et al, 2008 [174]	Meta-analysis	-	10 studies including 1470 children: 562 children with OSAS, 815 healthy children, and 93 children with juvenile	In three studies, 193 patients with OSAS, 93 children with juvenile rheumatoid arthritis and with 815

			rheumatoid arthritis	healthy children were compared using the Child Health Questionnaire (CHQ). Children with OSAS had poorer scores in 8 of 12 CHQ subscale scores than controls. Children with OSAS had poorer scores in the parental impact-emotional subscale than healthy controls. Children with OSAS were similar to patients with juvenile rheumatoid arthritis regarding quality of life scores. In seven studies, 369 children with OSAS underwent adenotonsillectomy and the OSA-18 total and subscale scores improved significantly ($P < 0.0001$). Improvement persisted at long-term follow-up.
Garetz et al, 2008 [259]	Systematic review	-	25 articles with sample sizes of 19 to 297 subjects with SDB who underwent adenotonsillectomy; 10 studies evaluated postoperative changes in quality of life, 4 studies changes in behavior, and 3 studies in neurocognitive skills; 5 studies evaluated changes in behavior and cognition, and 2 studies examined improvements in behavior and quality of life; 1 study evaluated changes in cognition, behavior, and quality of life.	All studies demonstrated improvements in quality of life, behavioral problems (including hyperactivity and aggression), and neurocognitive skills (memory, attention, or school performance). There is poor correlation between improvements in outcome measures and polysomnographic variables.
vi) risk factors for persistence of OSAS				
Li et al, 2013 [191]	Prospective, population-based, cohort study	I	70 children (60% boys) with ages 6-13 years and a diagnosis of primary snoring in a previous community-based study evaluating the prevalence of OSAS were invited for repeat polysomnography 4 years later (mean age 14.7 ± 1.8 years; 60% boys).	OSAS was defined as obstructive AHI ≥ 1 episodes/h. Mean duration of follow-up was 4.6 ± 0.6 years. On repeat polysomnography, 26 subjects (37.1%) had progressed to OSAS and 5 (7.1%) of them had moderate to severe disease (OAHI ≥5 episodes/h). 22 (31.4%) children had persistent primary snoring and 18 (25.7%) had complete resolution of snoring with normal polysomnogram. Multivariate logistic regression analysis demonstrated that persistent overweight/obesity was a significant risk factor for the progression to OSAS (OR 7.95; 95% CI 1.43-44.09).
Marcus et al, 2013 [192]	Randomized controlled multicenter trial early adenotonsillectomy versus watchful waiting	I	464 (5-9 y.o.), 46% children in the watchful waiting group and 48% in the early treatment group were overweight	The two groups did not differ regarding change in the Developmental Neuropsychological Assessment from

			or obese. Polysomnographic, cognitive, behavioral, and health outcomes were evaluated at baseline and at 7 months.	baseline to follow-up (P=0.16). There were significantly greater improvements in behavioral, quality-of-life, and polysomnographic outcomes and greater symptom reduction in the early-adenotonsillectomy group compared to the watchful-waiting group. Normalization of polysomnographic findings (AHI <2 episodes/h) was observed in a larger proportion of children in the early-adenotonsillectomy group than in the watchful-waiting group (79% vs. 46%). In the watchful-waiting group, spontaneous OSAS resolution was more common in nonblack children (P <0.01), nonobese children (P <0.001), and children with a baseline AHI ≥4.7 episodes/h (P <0.001).
Goodwin et al, 2010 [193]	Prospective, population-based, cohort study	I	319 children had 2 polysomnograms at home approximately 5 years apart. The mean age at first evaluation was 8.5 years (range 6-12), and mean age at second assessment was 13.7 years (range 10-18).	SDB was defined as a respiratory disturbance index ≥1 episode/h associated with oxygen desaturation ≥3%. Body mass index percentiles were calculated. Incident SDB was more frequent in boys (OR 3.93; 95% confidence interval 1.41-10.90; P=0.008). Children with prevalent SDB were more likely to be boys (OR=2.48; P=0.006) and had a greater increase in body mass index percentile (OR 1.01; P=0.034). Children with prevalent SDB had 3.41 greater odds for development of obesity from baseline to follow-up compared to children with prevalent No SDB.
Li et al, 2010 [194]	Prospective, population-based, cohort study	III	45 children identified with mild OSAS (AHI 1-5 episodes/h) in a previous community-based study of subjects with ages 6-13 y.o. evaluating the prevalence of OSAS underwent repeat polysomnography 2 years later	In 13 of 45 (29%) children OSAS severity worsened (increase in obstructive AHI >2.38 episodes/h). Compared to children in whom OSAS severity did not worsen, the worsened OSAS group had greater increase in waist circumference, higher frequency of tonsillar hypertrophy at baseline and follow-up visits, and higher prevalence of habitual snoring at baseline and follow-up evaluations. Multivariate analysis demonstrated that change in obstructive AHI was associated significantly with age at baseline (P = 0.009), male gender (P<0.001), presence of tonsillar hypertrophy at baseline (P =

				0.001), change in waist circumference (P = 0.002) and persistent tonsillar hypertrophy over the 2-year period (P<0.001).
c. *When polysomnography is not available, treatment has been considered when an alternative diagnostic method indicates OSAS or SDB-associated morbidity is present.*				
Author, year	**Type of Study**	**Class**	**Subjects**	**Methods and findings**
Certal et al, 2015 [211]	Systematic review and meta-analysis	-	Ten diagnostic studies with 724 patients were included in the systematic review, which was followed by a meta-analysis of 4 studies.	The analysis of two studies (76 patients) revealed a moderate sensitivity of 76%, a moderate specificity of 76% and a pooled diagnostic odds ratio of 15.18 (95% CI: 3.52–65.43). Using a cutoff of AHI >1 for the diagnosis of OSAS and based on the analysis of two studies (37 patients), the sensitivity was 88% and the specificity 71%.
Garetz et al, 2015 [173]	Multicentre, single-blind, randomised, controlled trial	I	464 children (5-9 y.o.) with OSAS randomly assigned to early adenotonsillectomy (median baseline obstructive AHI 4.8 episodes/h) or watchful waiting (median baseline obstructive AHI 4.5 episodes/h). OSAS was defined as an obstructive AHI ≥2 episodes/h or an obstructive apnea index ≥1 episode/h. The Pediatric Quality of Life inventory, the Sleep-Related Breathing Scale of the Pediatric Sleep Questionnaire, the 18-item Obstructive Sleep Apnoea QoL instrument, and the modified Epworth Sleepiness Scale were completed before adenotonsillectomy and at 7 months postoperatively.	Greater improvements regarding most measures of quality of life and symptom severity were demonstrated in the early adenotonsillectomy group than in the watchful waiting arm. There was weak correlation between improvement in polysomnography indices and changes in quality of life or symptom severity measures. Baseline OSAS severity did not influence the association between quality of life or symptom severity measures and treatment arm.
Rosen et al, 2015 [246]	Multicenter, single-blind, randomized, controlled trial	I	464 children (5-9 y.o.) with OSAS randomly assigned to early adenotonsillectomy (median baseline obstructive AHI 4.8 episodes/h) or watchful waiting (median baseline obstructive AHI 4.5 episodes/h). Baseline and 7-month follow-up data were analysed from 185 children in the early adenotonsillectomy arm. Associations were assessed between baseline Pediatric Sleep Questionnaire score or AHI and postoperative changes in the NEPSY and executive function, behavior, quality of life and sleepiness as rated by parents.	Higher baseline Pediatric Sleep Questionnaire scores-but not the baseline AHI- predicted postadenotonsillectomy improvement in executive functioning, behavior, quality of life, and sleepiness as rated by parents. Neither the Pediatric Sleep Questionnaire nor polysomnographic parameters were associated with objectively assessed executive dysfunction (NEPSY score) or its improvement postoperatively.
Horwood et al, 2014 [215]	Retrospective, cohort study	IV	362 children (median age 4.8 years; interquartile range 3.3-6.7 years; 61%	Two-hundred-sixty-six (73%) had inconclusive oximetry and 96 (27%) had

			male) with adenotonsillar hypertrophy and suspected OSAS who underwent pulse oximetry with analysis based on the McGill oximetry score.	abnormal oximetry. 30% of children with inconclusive oximetry and 83% of those with abnormal oximetry underwent adenotonsillectomy. No child with an inconclusive oximetry required hospitalization for more than 1 night postoperatively whereas 14% of patients with an abnormal oximetry required hospitalization for 2 or 3 nights (P = 0.001). Frequencies of readmissions and emergency department visits were low regardless of inconclusive or abnormal oximetry results.
Saito et al, 2007 [202]	Prospective cohort study	III	232 children (1.4-10 y.o.) with symptoms indicative of SDB and 25 healthy children as controls.	All children had nocturnal oximetry and 86 of them underwent adenotonsillectomy and follow-up oximetry.Mean oxygen desaturation index (≥3%-ODI3) in controls was 0.74 episodes/h ± 0.65 episodes/h. Also mean oxygen desaturation index (≥4%-ODI4) was 0.21 ± 0.29 episodes/h. Improvements in ODI3 and ODI4 after adenotonsillectomy correlated significantly with preoperative values. 95% of subjects with ODI3 ≥ 3.5 episodes/h and/or ODI4 ≥ 1.5 episodes/h had improvement in the respective indices > twice the standard deviation in controls.

Question 5.2. Is the treatment of primary snoring beneficial?				
Author, year	**Type of Study**	**Class**	**Subjects**	**Methods and findings**
Biggs et al, 2014 [212]	Review	-	13 studies with primary snoring confirmed by polysomnography.	Children with primary snoring have similar cognitive deficits and behavioral abnormalities to those in children with OSAS.
Li et al, 2013 [191]	Prospective, population-based, cohort study	I	70 children (60% boys) with ages 6-13 years and a diagnosis of primary snoring in a previous community-based study evaluating the prevalence of OSAS were invited for repeat polysomnography 4 years later (mean age 14.7 ± 1.8 years; 60% boys).	OSAS was defined as obstructive AHI ≥ 1 episodes/h. Mean duration of follow-up was 4.6 ± 0.6 years. On repeat polysomnography, 26 subjects (37.1%) had progressed to OSAS and 5 (7.1%) of them had moderate to severe disease (OAHI ≥5 episodes/h). 22 (31.4%) children had persistent primary snoring and 18 (25.7%) had complete resolution of snoring with normal polysomnogram. Multivariate logistic regression analysis

				demonstrated that persistent overweight/obesity was a significant risk factor for the progression to OSAS (OR 7.95; 95% CI 1.43-44.09).
Li et al, 2009 [111]	Cross-sectional, community-based study	IV	90 children (6-13 y.o.); 56 nonsnoring controls, 46 children with primary snoring, 62 children with AHI 1-3 episodes/h, and 26 children with an AHI > 3 episodes/h	Nocturnal sleep study and ambulatory blood pressure monitoring were carried out. Nocturnal diastolic blood pressure was significantly higher in children with primary snoring compared to controls after adjustment for age, gender, and body mass index.
Marcus et al, 1998 [269]	Prospective, cohort study	IV	Of 75 children with primary snoring (snoring, obstructive apnea index <1 episode/hour, normal gas exchange, and infrequent arousals), 20 were available for re-evaluation 1-3 years after the initial diagnosis of primary snoring (mean age 6 ± 4 years)	Initial apnoea index was 0.2 ± 0.3 episodes/h, SpO_2 nadir 95 ± 2%, and peak end-tidal PCO_2 was 47 ± 3 mmHg. All children had parental report of snoring at the time of follow-up evaluation. Overall, there were no significant changes in apnoea index, SpO_2, or peak end-tidal PCO_2, but four children had mild OSAS on repeat polysomnography.

Question 5.3. Are there conditions predisposing to upper airway obstruction which make treatment of obstructive SDB a priority?				
a. *Major craniofacial abnormalities*				
Author, year	**Type of Study**	**Class**	**Subjects**	**Methods and findings**
Zandieh et al, 2013 [270]	Retrospective, cohort study	IV	47 patients with syndromic craniosynostosis and age <21 years (66 % Apert syndrome; 19 % Pfeiffer syndrome; 15 % Crouzon syndrome).	Mean age of participants at first visit was 1.2 ± 3.3 years and they were followed for a mean of 14.6 ± 8.6 years. Of children with at least 1 sleep study, 83% had OSAS (severe in 42% of cases, moderate in 19% and mild in 22). Adenotonsillectomy was performed in 62% of patients and preoperative and postoperative polysomnography was carried out in 45% of them. Postoperatively, the mean AHI did not change significantly and OSAS persisted in 11 of 13 patients.
Amonoo-Kuofi et al, 2009 [271]	Retrospective, cohort study	IV	26 with syndromic craniosynosotosis and mean age 4.5 years (range, 1.6-13.9 y)	Seven subjects had severe OSAS, 11 had moderate OSAS, and 7 had mild OSAS based on a clinical sleep severity score prior to adenotonsillectomy. 60% demonstrated improvement in sleep severity score postoperatively.
Spier et al, 1986 [272]	Retrospective, cohort study	IV	8 patients (8-22 y.o.) with Pierre-Robin	Patients underwent polysomnography. 7

			syndrome	of 8 patients had significant but of minor degree sleep disturbance and apneas, and less time spent in REM sleep. One patient who had undergone mandibular surgery demonstrated a central apnoea index of 81.7 episodes/h and an obstructive sleep apnoea index of 1.9 episodes/h. The patients had small mandibles and mildly increased right ventricular diastolic dimensions (M-mode echocardiography). Snoring was present in all cases.
b. *Neuromuscular disorders*				
Author, year	**Type of Study**	**Class**	**Subjects**	**Methods and findings**
Hsiao et al, 2008 [273]	Retrospective, cohort study	IV	19 children with cerebral palsy and clinical OSAS	Parents completed a structured questionnaire for the assessment of child's quality of life and symptoms of OSAS (OSA-18) before and after treatment (adenotonsillectomy or nasal CPAP; n=10) or over a 6-month period in controls with cerebral palsy and OSAS who did not receive treatment (n=9). The treatment group improved in symptoms of OSAS and there was a trend for improvement in quality of life.
Kerschner et al, 2002 [274]	Retrospective case-series	IV	15 children (1-15 y.o.; 11 boys) with neurological impairment and clinical OSAS	Treatment consisted of adenotonsillectomy and uvulopalatopharyngoplasty. Primary area of obstruction in the posterior oropharynx (soft palate, pharyngeal walls and base of tongue). Pre-postoperative oximetry (n=13) showed significant improvement in mean lowest oxygen saturation from 65% preoperative to 85% postoperative (P=0.005). In long-term follow-up (5.2 years), 77% (10 of 13) of those showing initial improvement did not require additional airway intervention.
Magardino et al, 1999 [275]	Retrospective case series	IV	25 children with cerebral palsy (11 months to 22 y.o.) and clinical OSAS	Long-term outcomes were based on parental reports. 84% had symptomatic improvement with tonsillectomy, adenoidectomy and/or uvulectomy and tracheostomy was avoided. Four children ultimately required a tracheotomy.
Cohen et al, 1997 [276]	Prospective, cohort study	IV	18 children (age 9 months-17.5 years) with cerebral palsy and severe refractory OSAS who underwent surgical treatment for OSAS	Pre- and postoperative polysomnography was obtained in 13 patients. 83% of children with indication for tracheostomy ultimately avoided the procedure (mean

				follow-up time 30 months). 26 procedures were performed in 18 patients. Adenotonsillectomy was required in 9 patients, turbinectomy and/or septoplasty in 9, tongue-hyoid advancement was completed in 13, uvulopalatoplasty in 13, conventional mandibular advancement in 2, distraction osteogenesis of the mandible in 2, and tongue reduction in 7 patients. Mean AHI decreased and SpO_2 nadir increased postoperatively.
Melacini et al, 1996 [116]	Cross-sectional study	IV	21 wheelchair-bound patients with Duchenne muscular dystrophy (10-24 years old)	Patients underwent electrocardiogram and echocardiogram, spirometry, daytime arterial blood gas analysis, and nocturnal SpO_2 monitoring. Patients were classified into: group A normoxaemic (14 subjects) and group B with nocturnal hypoxaemia (7 cases). Group A was divided into 2 subgroups, one without (n=9; ejection fraction 56%), and one with left ventricular dilation (n=5; ejection fraction 32%). Analysis of pulsed Doppler pulmonary data indicated significant reduction in corrected time to peak velocity in group B patients, when compared with controls, A1, and A2 groups respectively. In group A, there was a correlation between ejection fraction and corrected time-to-peak velocity. Two patterns of cardiac involvement may be recognized in advanced-stage Duchenne muscular dystrophy: left ventricular wall motion abnormalities and dilated cardiomyopathy. Doppler data probably suggesting pulmonary hypertension may be observed in patients with dilated cardiomyopathy, and in patients with nocturnal hypoxaemia.
c. *Achondroplasia*				
Author, year	**Type of Study**	**Class**	**Subjects**	**Methods and findings**
Julliand et al, 2012 [277]	Prospective, cohort study	IV	30 children (median age 3.0 years, range: 0.4-17.1) with achondroplasia	Habitual snoring and witnessed apneas were noted in 77% and 33% of children, respectively. Upper airway surgery had been performed in 34% and craniocervical decompression procedure in 17% of them. Arterial blood gases were abnormal in two (7%) patients. 93% of children had abnormal polysomnography. 37% of patients had

				AHI ≥1 episode/h and 87% had AHI ≥5 episodes/h. Oxygen desaturation of haemoglobin index (≥3) was >5 episodes/h in 73% of children. Two (7%) patients had a maximum nocturnal transcutaneous carbon dioxide pressure>50 mmHg. Additional therapeutic interventions included upper airway surgery and noninvasive positive pressure ventilation.
Afsharpaiman et al, 2011 [51]	Retrospective cohort study	IV	46 children with achondroplasia aged 3 months-14 years	54.3% of patients had OSAS (AHI >5 episodes/h). The follow-up period for 19 children was 3 months-11 years. 13 patients underwent adenotonsillectomy and 9 required CPAP.
Sisk et al, 1999 [53]	Retrospective, cohort study	IV	95 children with achondroplasia aged 1 day to 14 years	OSAS was diagnosed clinically in 36 children (38%). Polysomnography was completed in 28 patients. Adenotonsillectomy was performed in 22 patients, and 18% of them required further treatment (additional surgery or CPAP). 10 patients underwent adenoidectomy alone and 90% of them required further surgery for recurrent OSAS. 2 children had tonsillectomy only and one of them required additional adenoidectomy.
Mogayzel et al, 1998 [54]	Retrospective, cohort study	IV	88 children with achondroplasia (1 month- 1.6 years old)	5 children had history of tracheostomy and 7 children were receiving supplemental oxygen prior to performance of polysomnography. 47.7% of subjects had abnormal polysomnography. Median obstructive apnoea index was 0 (0- 19.2 episodes/h) and median number of central apneas with desaturation was 0.5 (0-49 episodes/h). The median SpO_2 nadir was 91% (50-99%), and the median peak end-tidal pCO_2 was 47 mm Hg (36-87 mm Hg). 2 additional children were treated with CPAP, and 2 additional subjects underwent tracheostomy.
Waters et al, 1995 [278]	Retrospective, cohort study	IV	30 subjects with achondroplasia (15 females) and median age 6.6 years (range 1.0-47.6) underwent polysomnography	Treatment interventions for OSAS in 17 subjects included adenotonsillectomy (n = 3), weight loss (n = 1), and CPAP (n = 13). 11 of 30 patients had overnight sleep study before and after treatment for OSAS. Respiratory disturbance index decreased from 38.4 ± 6.9 to 6.5 ± 1.8

				events/h (P < 0.001) and obstructive events from 33.7 ± 6.9 to 2.4 ± 1 events/h (P < 0.001).
Ryken et al, 1994 [279]	Retrospective, cohort study	IV	6 patients with achondroplasia and symptoms of cervicomedullary junction compression (3 females; average age 8 years and range 7 months-30 years).	Mean duration of symptoms prior to surgical intervention was 1.9 years. Symptoms included occipitocervical pain, ataxia, incontinence, apnea, and respiratory arrest. Findings in imaging studies included severe stenosis of foramen magnum, ventrolateral cervicomedullary junction compression secondary to central and paramesial basilar invagination, and dorsal cervicomedullary junction compression secondary to ligamentous hypertrophy and invagination of the posterior atlantal arch. Symptoms improved after dorsal decompression of the craniovertebral junction.
d. *Chiari malformation*				
Author, year	**Type of Study**	**Class**	**Subjects**	**Methods and findings**
Addo et al, 2013 [280]	Retrospective, cohort study	IV	5 children with Chiari malformation type I, syndromic craniosynostosis and central apnea; 2 patients had Crouzon syndrome and 3 patients had Pfeiffer syndrome.	All children underwent foramen magnum decompression and polysomnography before and after surgery. Age at the time of surgery was 1.1 to 12.6 years (median age 4.1 years). The median postoperative follow-up was 3.6 years. Two children had a > 80% reduction in the number of central sleep apneas at 1.5 and 21 months after decompression. The other 3 children had a > 60% reduction in the number of central sleep apnoeas between 2 and 10 months after decompression. The central apnoea index improved in all patients.
Khatwa et al, 2013 [58]	Retrospective, cohort study	IV	22 children with Chiari malformation type I (11 males median age 10 years, range 1-18 years)	3 children had central sleep apnea, 5 had OSAS and one child had both obstructive and central sleep apnoeas. Children with SDB had excessive crowding of the brainstem structures at the foramen magnum and greater length of herniation relative to children without SDB. Patients with central sleep apneas underwent surgical decompression, with improvement in polysomnography.
Bell et al, 1987 [281]	Retrospective, cohort study	IV	22 patients with repaired myelomeningoceles, shunted hydrocephalus, and symptomatic Arnold-Chiari malformations (17 ≤ 6	Symptoms in infants were stridor, apnoea or feeding difficulty; Symptoms in older patients were hemiparesis, quadriparesis, oscillopsia, nystagmus, or opisthotonos.

			m.o.; 5 patients 3-23 y.o.)	14 infants underwent surgical decompression of the Arnold-Chiari malformation. Of 10 infants who underwent early surgery, 3 became asymptomatic, 2 improved and 5 died. 4 infants had late surgery: 2 died and 2 had partial or complete resolution of symptoms. 3 infants did not have surical decompression: 2 died and 1 improved. 5 older patients who underwent decompression had complete resolution of the preoperative clinical manifestations.
e. *Down syndrome*				
Lin et al, 2014 [282]	Retrospective, cohort study	III	49 children with Down syndrome referred for polysomnography ; 49 otherwise healthy children suspected for OSAS matched for gender, age, and SDB severity who underwent polysomnography during the same period (46 females; mean age of all participants 6.2 years (range 0.3-16.9 years); a cohort of 278 typically developed children referred for polysomnography was also included for comparison.	Parents completed a SDB symptom questionnaire. Children with Down syndrome had median obstructive AHI 6.1 episodes/h (range 0-38 episodes/h) in the Down syndrome group and 6.5 episodes/h (range 0-30 episodes/h) in the control group (P = 0.87) Children with Down syndrome had more severe OSAS compared to 278 typically developing children (P<0.001). Symptom scores were not different between the matched groups. Participants with Down syndrome had higher average pCO_2 during sleep (P = 0.02) and worse McGill oximetry scores.
Shete et al, 2010 [283]	Retrospective, cohort study	III	11 children with Down syndrome (mean age 101 months; 64% males; average BMI 29.8) and 9 children without Down syndrome (mean age 80 months; 88% males; average BMI 27.6).	Polysomnography was performed before and after adenotonsillectomy. AHI decreased significantly after adenotonsillectomy especially in children without Down syndrome. REM-AHI and lowest SpO_2 did not change significantly in children with Down syndrome as opposed to children without Down syndrome. 73% of patients with Down syndrome required CPAP, NPPV or oxygen for persistent OSAS.
de Moura et al, 2008 [284]	Prospective, cohort study	III	24 children with Down syndrome (4-14 y.o.) were randomly allocated to undergo rapid maxillary expansion or not.	Parents of patients who underwent rapid maxillary expansion reported a reduction in respiratory obstruction symptoms. Cephalometry demonstrated increased maxillary width in the rapid maxillary expansion group.
Merrell et al, 2007 [285]	Retrospective, cohort study	IV	21 children with Down syndrome (mean age 3.7 y.o.) who had adenoidectomy	Polysomnography was carried out before and after surgery. 67% of participants

			and tonsillectomy; 16 children with Down syndrome of similar age who were treated with adenoidectomy, tonsillectomy and lateral pharyngoplasty	with adenoidectomy and tonsillectomy had elevated AHI, hypoxaemia or hypercapnia, postoperatively; 75% of children undergoing adenoidectomy, tonsillectomy and pharyngoplasty had elevated AHI, hypoxemia or hypercapnia after surgery. There were no statistically significant differences in the outcomes between the two groups.
Jacobs et al, 1997 [286]	Retrospective, cohort study	IV	18 patients with chronic airway obstruction who developed pulmonary hypertension	Pulmonary artery hypertension was diagnosed by cardiac catheterisation in 13 patients and by echocardiography in 5 patients. Chronic airway obstruction was due to chronic lung disease in 9 patients, tracheobronchomalacia in 6 patients, adenotonsillar hypertrophy in 5 patients, laryngomalacia in 4 patients, macroglossia in 5 patients, subglottic stenosis in 2 patients), and pharyngeal collapse in 2 patients. 9 patients had history of prematurity and 7 had Down syndrome. Treatment interventions included tracheotomy in 7 subjects, adenotonsillectomy in 5 subjects, adenoidectomy in 3 subjects, laser epiglottoplasty in 1subject, and supplemental oxygen in 12 subjects. Pulmonary hypertension improved in 14 patients and worsened in 4 patients, 3 of whom died.
Lefaivre et al, 1997 [114]	Prospective, cohort study	IV	7 children with Down syndrome and OSAS (2 girls; 3-12 years old)	Surgical treatment for OSAS included tongue reduction (n = 6), tongue-hyoid advancement (n = 4), uvulopalatopharyngoplasty (n = 7), and maxillary or midface advancement (n = 2); 1 child was intubated preoperatively for respiratory failure, he was later found to have pulmonary hypertension and ultimately underwent tracheostomy. Patients had preoperative and postoperative nocturnal polysomnography and radiologic evaluation to assess the efficacy of surgical treatment in OSAS. Clinical manifestations of OSAS, apnoea index, respiratory disturbance index, SpO_2 nadir, and surgical morbidity were the main outcome measures. 6 children had both preoperative and postoperative polysomnography. Mean apnoea index and respiratory disturbance index were

				34 episodes/h and 52.46 episodes/h preoperatively compared to 1.62 episodes/h and 6.46 episodes/h, respectively after surgery.All children with Down syndrome improved regarding snoring, noisy breathing, and oxygen requirements.
Jacobs et al, 1996 [115]	Retrospective, cohort study	IV	71 pediatric patients with Down syndrome and upper airway obstruction over a 5-year period	34 children had pulmonary arterial hypertension; 44 of 71 patients had multiple sites of airway obstruction. Abnormalities causing airway obstruction included included lymphoid hyperplasia, macroglossia, narrow nasopharynx, laryngomalacia, congenital subglottic stenosis, tracheobronchomalacia, and tracheal stenosis. Children with upper airway obstruction underwent surgical procedures including tonsillectomy, adenoidectomy, tonsillar pillar plication, uvulopalatopharyngoplasty, anterior tongue reduction, tongue-hyoid suspension, laryngotracheoplasty, and tracheotomy. 27 patients had mild obstructive symptoms, and most of them improved after tonsil or adenoid surgery, or both. The remaining patients were of younger age and had more severe symptoms, multiple sites of obstruction, and high incidence of cardiac disease. 11 (39%) of the 28 patients in this group had significant residual symptoms after surgery. Four children are tracheotomy-dependent. 5 deaths occurred and 3 of them were attributed to upper airway obstruction.
Bower et al, 1995 [287]	Retrospective, cohort study	IV	16 patients with Down syndrome (mean age 4.9 years; range 1-14 years)	15 of 16 patients had upper airway obstruction related to adenotonsillar hypertrophy and 1 had adenoidal hypertrophy. Surgical procedures included: tonsillectomy and adenoidectomy (n=13), adenoidectomy (n=1), tonsillectomy (n=1), and uvulopalatopharyngoplasty /adenoidectomy (n=1). 4 patients (25%) required observation in an intensive care setting postoperatively. Average hospital stay was 2.1 days (range 0-7 days). Significant postoperative apnoea was common, and oxygen was used in over 60% of patients. Symptoms resolved in

				69% of patients at last follow up.
f. *Mucopolysaccharidoses*				
Author, year	**Type of Study**	**Class**	**Subjects**	**Methods and findings**
Mesolella et al, 2013 [69]	Retrospective, cohort study	IV	20 patients (7 female; median age 6 years at the beginning of the observation period) with mucopolysaccharidosis (35% type I; 30% type II; 20% type III; 5% type IV; 10% type VI)	Recurrent otitis media was recorded in 30% of cases, hearing loss in 75%, adenotonsillar hypertrophy in 75%, frequent infections of the upper airway in 75% and OSAS in 45% of cases. 50% of participants underwent surgical therapy (adenotonsillectomy, adenoidectomy with insertion of middle ear ventilation tubes, tonsillectomy, tracheotomy and resection of vocal cord polyps).
John et al, 2011 [70]	Cross-sectional study	IV	28 children with mucopolysaccharidosis type VI (mean age 98.5 months; 14 boys)	Main symptoms and signs included: snoring, apnea, pectus carinatum, and macroglossia. 85.1% of subjects had OSAS (AHI > 1.5 episodes/h). Mean AHI was 19.84 ± 26.25 episodes/h. Pulmonary hypertension was demonstrated in 14 patients by echocardiography and was associated with SpO_2 nadir.
Lin et al, 2010 [71]	Cross-sectional study	IV	24 patients with mucopolysaccharidosis (2 females; 3 with type I, 15 with type II, 1 with type III, 1 with type IV, and 4 with type VI; mean age, 10.8 ± 6 years; age range, 2.0-23.7 years)	Nadir SpO_2 was 74.5 ± 12.3%, and average % sleep time with SpO_2 <95% was 39.4%. Respiratory disturbance index was 21.8 ± 20.4 episodes/h, obstructive AHI was 21.4 ± 19.9 episodes/h, central apnea index was 0.4 ± 0.6 episodes/h and desaturation index was 17.6 ± 17.8 episodes/h. The prevalence of moderate to severe OSAS was 88%. Enzyme replacement therapy in 2 patients with mucopolysaccharidosis type II was accompanied by reduction in RDI.
Nashed et al, 2009 [288]	Retrospective, cohort study	IV	11 children (age 5.2 years; range 0.8-17.8 years) with mucopolysaccharidosis	Polysomnography was performed before and after treatment for OSAS (obstructive AHI >1.5 episodes/h). Obstructive AHI was 6.6 (0.0-54.8) episodes/h and central apnoea index was 0.6 (0.0-2.6) episodes/h; 7 children had OSAS and 3/7 children were classified as having severe OSAS (obstructive AHI > 10 episodes/h); 5 of 7 children underwent treatment for OSAS and 3 of them had reduction in obstructive AHI. Two patients with OSAS improved with enzyme replacement treatment.

g. *Prader-Willi syndrome*				
Author, year	**Type of Study**	**Class**	**Subjects**	**Methods and findings**
Cohen et al, 2014 [73]	Retrospective, cohort study	IV	44 patients with Prader-Willi (0.3-15.6 years old; 23 subjects <2 years of age)	Children <2 year old had more frequently central sleep apnoea compared to older children (43% vs. 5%; P = 0.003). Obstructive events were prevalent in older children than in younger children (52% vs. 5%, respectively; P = 0.001). Supplemental oxygen was used in 9 infants with Prader-Willi syndrome and central sleep apnoea. Median central apnea index decreased from 14 to 1 episode/h (P = 0.008).
Sedky et al, 2014 [74]	Quantitative review	-	14 studies of children with Prader-Willi syndrome (0-17.8 y.o.) who underwent polysomnography in order to exclude OSAS (n = 224 children)	Prevalence of OSAS across studies was 79.91% (179/224); 53.07% had mild OSAS, 22.35% moderate OSAS, and 24.58% severe OSAS. Younger children and those with higher BMI z scores had higher AHI. Narcolepsy was present in 35.71% of cases. Adenotonsillectomy was associated with improvement in OSAS for most children but residual OSAS was present in the majority of cases postoperatively.
Vandeleur et al, 2013 [75]	Retrospective, cohort study	IV	34 children with Prader-Willi syndrome (age 3 months-16.3 years) who underwent polysomnography over a period of 8 years prior to initiation of treatment with growth hormone	15 of 34 children had OSAS (obstructive AHI > 1 episode/h). Patients with OSAS were significantly older (P = 0.009) and more likely to have hypertrophic tonsils (P = 0.05) compared to participants without OSAS. The two groups did not differ in BMI z-score or frequency of OSAS symptoms.
Al-Saleh et al, 2013 [289]	Retrospective, cohort study	IV	15 children with Prader-Willi syndrome (median age 3.7 years; range, 0.8-15.4 years; median body mass index percentile was 82.4; range, 0-100).	Patients underwent polysomnography before and at 6 weeks, 6 months, 1 year, and 2 years after initiation of therapy with growth hormone. Growth hormone was discontinued in 2 children due to development of severe OSAS during the first 6 weeks of treatment. All other children were followed for up to 2 years while receiving treatment without development of obstructive or central sleep apnoea.
Miller et al, 2009 [290]	Retrospective, cohort study	IV	20 patients with Prader-Willi syndrome (age 2-21 months)	Overnight polysomnography was performed before and 6 weeks after initiation of growth hormone therapy. Overall, there were no significant changes in respiratory events during sleep before and after growth hormone

				therapy. 5 patients had a decrease in the frequency of obstructive events while 5 patients had an increase in the frequency of obstructive events in conjuction with upper respiratory infection or gastroesophageal reflux.
Tauber et al, 2008 [291]	Case-control study	II	64 cases of death in children with Prader-Willi syndrome (22 females; aged from a few days to 19 years) were identified, 28 of whom received treatment with growth hormone	Respiratory failure or infection were the most common causes of death and were reported in 61% of all children (68% in those treated with growth hormone and 55.5% in untreated patients). There were no significant differences in gender, frequency of obesity or OSAS between the two study groups. 75% of deaths in patients receiving growth hormone occurred during the first 9 months following initiation of treatment. There was high frequency of respiratory infections in both GH-treated and -untreated PWS children.

Question 5.4. Are children at risk for obstructive SDB but with negative polysomnography usually re-evaluated?				
Author, year	**Type of Study**	**Class**	**Subjects**	**Methods and findings**
Li et al, 2013 [191]	Prospective, population-based, cohort study	I	70 children (60% boys) with ages 6-13 years and a diagnosis of primary snoring in a previous community-based study evaluating the prevalence of OSAS were invited for repeat polysomnography 4 years later (mean age 14.7 ± 1.8 years; 60% boys).	OSAS was defined as obstructive AHI ≥ 1 episodes/h. Mean duration of follow-up was 4.6 ± 0.6 years. On repeat polysomnography, 26 subjects (37.1%) had progressed to OSAS and 5 (7.1%) of them had moderate to severe disease (OAHI ≥5 episodes/h). 22 (31.4%) children had persistent primary snoring and 18 (25.7%) had complete resolution of snoring with normal polysomnogram. Multivariate logistic regression analysis demonstrated that persistent overweight/obesity was a significant risk factor for the progression to OSAS (OR 7.95; 95% CI 1.43-44.09).

Online Supplementary Table 6.

Step 6: Stepwise treatment approach for SDB in childhood

Question 6.1. Is there evidence that treatment interventions for obstructive SDB in childhood should follow a stepwise approach?

Author, year	Type of Study	Class	Subjects	Methods and findings
Hartzell et al, 2013 [292]	Retrospective, cohort study	IV	7 children (mean age 6.0 years) who underwent combined adenotonsillectomy, uvulopalatopharyngoplasty, and tongue-base suspension; 7 patients (mean age 6.3 years) underwent adenotonsillectomy and uvulopalatopharyngoplasty.	Children who underwent tongue-base suspension had mean preoperative AHI 27.2 episodes/h and those who did not undergo this procedure had AHI 6.8 episodes/h. The mean decrease in AHI was 16.5 episodes/h in the tongue-base suspension group and 5.0 episodes/h in the group without tongue-base suspension. The mean oxygen saturation nadir improved in both groups. No complications occurred.
Guilleminault et al, 2011 [293]	Prospective, cohort study	II	31 children (mean age 6.5 years; 14 boys) diagnosed with OSAS based on symptoms and polysomnography findings	Children were randomized to receive either adenotonsillectomy followed by rapid maxillary expansion (n=16; AHI 12.5±0.8 episodes/h) or rapid maxillary expansion followed by adenotonsillectomy (n=15; AHI 11.1±0.7 episodes/h). Both symptoms and polysomnography parameters improved after the first procedure (adenotonsillectomy or rapid maxillary expansion) but only one child achieved normal AHI. At the completion of both procedures both groups had similar AHI (0.9±0.3 episodes/h).
Cohen et al, 1997 [276]	Prospective, cohort study	IV	18 children (age 9 months-17.5 years) with cerebral palsy who underwent surgical treatment for OSAS	83% of children with indication for tracheostomy ultimately avoided the procedure (mean follow-up time 30 months). 50% of patients had adenotonsillectomy and 50% of children underwent turbinectomy and/or septoplasty in 9. Moreover, tongue-hyoid advancement was completed in 13, uvulopalatoplasty in 13, conventional mandibular advancement in 2, distraction osteogenesis of the mandible in 2, and tongue reduction in 7 patients. Mean AHI decreased and SpO_2 nadir increased postoperatively.

6.2. What are the indications and efficacy of weight loss in children with obstructive SDB?

Indications and efficacy of weight loss

Author, year	Type of Study	Class	Subjects	Methods and findings
Verhulst et al, 2009 [294]	Prospective cohort study	IV	61 obese teenagers (14.8 ± 2.3 y.o.; BMI z score 2.7 ± 0.4)	Multicomponent residential treatment program consisting of moderate dietary

				restriction (1,400–1,600 kcal/day), regular physical activity, group and individual psychological support, and medical supervision. Twenty-nine subjects (48%) had mild SDB and 8 subjects (13%) had moderate-to-severe SDB. After 5.2 ± 0.5 months of therapy, there was a median absolute decrease in BMI *z* score of 0.9 (range = 0.5–1.8) which corresponded to a median relative decrease of 35.8% (range = 16.2–76.3). AHI decreased to < 2 episodes/h in 62% of subjects with SDB before treatment; 91% of subjects had AHI < 5 episodes/h.
Kalra et al., 2005 [295]	Retrospective cohort study	IV	34 adolescents undergoing laparoscopic Roux en Y gastric bypass surgery	10 subjects had polysomnography before and after surgery. Significant weight loss occurred postoperatively (mean loss 58 kg) and median AHI reduced from 9.1 to 0.65 episodes/h; 95% of subjects with OSAS had AHI <5 episodes/h after surgery.
Siegfried et al., 1999 [296]	Retrospective cohort study	IV	38 extremely obese (mean BMI 45.3 ± 7.9 kg/m^2) adolescents	A residential weight loss program (3-9 months) led to mean BMI decrease from 45.3 to 35.8. The mean respiratory distrurbance index decreased from 4.08 to 3.27 episodes/h. Respiratory disurbance index of <5 episodes/h was achieved in 67% of subjects with respiratory disturbance index > 5 episodes/h before the weight loss.

6.3. What are the indications, efficacy and potential complications of nasal corticosteroids or montelukast in children with obstructive SDB?				
a+b+c. *Indications, efficacy, complications*				
Author, year	**Type of Study**	**Class**	**Subjects**	**Methods and findings**
Kheirandish-Gozal et al, 2014 [252]	Retrospective cohort study	IV	3,071 children (2-14 y.o.) were diagnosed with OSAS; in 836 of them OSAS was of mild severity.	Children with OSAS and obstructive AHI >5 episodes/h were referred for adenotonsillectomy or CPAP, while those with obstructive AHI >1 and <5 episodes/h were recommended treatment with an intranasal corticosteroid and oral montelukast for at least 12 weeks, following which a second overnight sleep study was performed to evaluate efficacy; 752 children received montelukast and intranasal corticosteroid; 445 patients underwent follow-up polysomnography; 62% of

				children with mild OSAS treated with a combination of oral montelukast and nasalcorticosteroid for 12 weeks had normal sleep studies at the end of the 12 weeks period (obstructive AHI <1 episode/h). Older (>7 y.o.) and obese children were significantly more likely to be non-responders (OR: 2.3; 95% CI: 1.43-4.13; P<0.001 and OR: 6.3; 95% CI: 4.23-11.18; P<0.000001, respectively).
Goldbart et al, 2012 [297]	Double-blind, randomized, placebo-controlled trial	I	46 children (> 2 and < 10 y.o with OSA and AHI < 10 episodes/h	23 children received placebo and 23 children received montelukast. The obstructive apnea index decreased by >50% in 65.2% of treated children.
Kheirandish-Gozal et al, 2008 [298]	Double-blind, randomized, crossover trial	II	62 children with mild OSA (age >6 and <12 years	Children with mild OSAS who received intranasal budesonide for 6 weeks improved in AHI, nadir oxygen saturation, sleep latency, slow-wave sleep, rapid-eye-movement sleep and adenoid size. The treatment effect persisted after discontinuation of budesonide for 8 weeks.
Berlucchi et al, 2007 [299]	Randomized, double blind, placebo-controlled trial	I	60 children who were assigned randomly to receive mometasone intranasally 50 mcg/nostril/day for 40 days (group A; n=30; 12 female subjects; median age: 5 years) or placebo (group B; n=30; 17 female subjects; median age: 4 years).	All children had chronic nasal obstruction symptoms, and >75% choanal obstruction by adenoidal hypertrophy on nasal endoscopy prior to the first stage of the study. In the second stage, patients in group A who had subjective and objective clinical improvement were divided into group A1 (11 children) who received topical intranasal steroid treatment on alternate days for the first 2 weeks of each month for 3 month, and subgroup A2 (10 children) who continued daily mometasone treatment for the first 2 weeks of each month for 3 months. 57 children completed the study according to the protocol. After the first stage, symptom severity and adenoidal size decreased for 21 patients (77.7%) in group A without improvement in group B. After 3 months of additional therapy, group A2 demonstrated a more-pronounced reduction in adenoidal size compared than group A1.
Goldbart et al, 2005 [300]	Prospective, cohort study	IV	24 children with mild SDB (5.4 ± 2.0 y.o.; range 2.5-10 y.o.; obstructive AHI	Children with SDB completed an open-label intervention with montelukast for

			3.0 ± 0.22 episodes/h); 16 control children with mild SDB (5.7 ± 1.8 y.o.; obstructive AHI 3.2 ± 0.2 episodes/h).	16 weeks. Polysomnography was repeated after completion of the intervention. Adenoidal size was evaluated with lateral X-ray films of the neck before and after treatment. Montelukast treatment induced significant reductions in adenoid size and AHI (2.0 ± 0.3 episodes/h; P = 0.017). In contrast, adenoidal size did not change in 16 control children with SDB who did not receive treatment and obstructive AHI increased (4.1 ± 0.4 episodes/h; P <0.03)
Brouillette et al, 2001 [301]	Randomized, triple-blind, placebo-controlled, parallel-group trial	I	25 children aged 1 to 10 years with moderate-to-severe OSA	13 children received fluticasone, and 12 received placebo. The mixed/obstructive AHI index decreased from 10.7 ± 2.6 (SE) episodes/h to 5.8 ± 2.2 in the fluticasone group but increased from 10.9 ± 2.3 to 13.1 ± 3.6 in the placebo group (P =0.04). The mixed/obstructive apnea/hypopnea index decreased in 12 of 13 subjects treated with fluticasone versus 6 of 12 treated with placebo; P =.03. Changes from baseline in tonsillar size, adenoidal size, and symptom score were not significantly different between groups.

6.4. What are the indications, efficacy and potential complications of adenotonsillectomy in children with obstructive SDB?				
a. *Indications and efficacy of adenotonsillectomy in otherwise healthy children*				
Author, year	**Type of Study**	**Class**	**Subjects**	**Methods and findings**
Burstein et al, 2013 [302]	Retrospective, cohort study	III	1- to 12-y.o. children who underwent polysomnography and adenotonsillectomy were matched by age, time since baseline sleep study and AHI to children who had polysomnography but did not undergo adenotonsillectomy.	All children had a clinical assessment score (CAS-15), follow-up polysomnography, and the Child Behavior Checklist (CBCL). 16 matched pairs of children completed the study. 63% of patients included in the adenotonsillectomy group patients and 88% of untreated patients were overweight or obese. The treated group was characterized by a greater median improvement in AHI compared to the untreated group (10.3% vs. 6.5%, P=0.044). Children with adenotonsillectomy were more likely to have a follow-up AHI<5 episodes/h (81% vs. 69%) and <1 episode/h (44% vs. 25%) but the differences were not

				statistically significant. The adenotonsillectomy group had significantly lower mean scores on the CAS-15 (8.9 ± 6.1 vs. 29.4 ± 16.2; P <0.001) and the CBCL total problem score (43.9 ± 8.7 vs. 58.9 ± 13.0; P<0.001).
Marcus et al, 2013 [192]	Randomized controlled multicenter trial early adenotonsillectomy versus watchful waiting	I	464 (5-9 y.o.) children with obstructive AHI≥2 episodes/h or an obstructive apnea index ≥1 episode/h; 46% children in the watchful waiting group and 48% in the early treatment group were overweight or obese.	At 7 months, significantly more children in the early intervention group (79%) had a postoperative obstructive AHI < 2 episodes/h and an obstructive apnoea index ,1 episode/h compared to the watchful waiting group (46%) (P< 0.001).
Alonso-Alvarez et al, 2012 [303]	Prospective, cohort study	IV	100 children (mean age 4.17 ± 2.05 years) who underwent adenotonsillectomy for OSAS.	Respiratory polygraphy was performed before and after adenotonsillectomy (7 months postoperatively). OSAS was defined as AHI ≥4.6 episodes/h. The effectiveness of adenotonsillectomy (defined as AHI<4.6 episodes/h) was 88.4% (95% CI 81–95.7%).
Bhattacharjee et al, 2010 [220]	Retrospective, multicenter study	IV	578 (mean age, 6.9 ± 3.8 years), 50.6% of subjects were obese	Polysomnography was performed before and after adenotonsillectomy and a significant AHI reduction from 18.2 ± 21.4 to 4.1 ± 6.4 episodes/h was demonstrated. 27.2% had complete resolution of OSAS defined as AHI< 1 episode/h after adenotonsillectomy.
Friedman et al, 2009 [250]	Updated systematic review and meta-analysis	-	1079 with age <20 years (mean sample size/study=42 with range of 10 to 199). Obese patients were not excluded. Complicated children were considered those with morbid obesity, severe OSAS or age <3-5 years.	The random-effects model estimate for treatment success (defined as AHI<1) after adenotonsillectomy was 59.8 % (95% CI 43.6%-74.0%; P=0.234). Cure rate was 73.8% in uncomplicated patients i.e. significantly higher than the cure rate of 38.7% in complicated patients (P<0.0001).
Brietzke et al, 2006 [251]	Meta-analysis	-	355 (mean sample size/study =28)	Random-effects model esimate for treatment success with adenotonsillectomy was 82.9 % (95% CI 76.2-89.5%; p< 0.001) (success criterion varied per individual article).
b. *Risk factors for OSAS persistence post-adenotonsillectomy*				
Author, year	**Type of Study**	**Class**	**Subjects**	**Methods and findings**
Huang et al, 2014 [304]	Prospective, cohort study	IV	Of 135 children (6-12 y.o.) who underwent adenotonsillectomy for OSAS, 88 were evaluated at 6, 12, 24 and 36 months postoperatively. These	Multivariate generalized linear modeling and hierarchical linear models analysis were applied to recognize predictors of suboptimal long-term resolution of

			88 children had a mean body mass index of 19.5 ± 4.6 kg/m^2 and a preoperative mean AHI of 13.54 ± 7.23 episodes/h.	OSAS, and generalized linear models were used for analysis of risk factors of OSAS recurrence. At 6 months, the mean postoperative AHI was 3.47 ± 8.41 episodes/h and 53.4% of children had AHI >1 episode/h. From 6 months to 36 months postoperatively, the AHI increased progressively to a mean AHI 6.48 ± 5.57 episodes/h and 68% of patients had AHI >1 episode/h. Presence of residual OSAS after adenotonsillectomy was significantly associated with higher BMI and AHI, and presence of enuresis, and allergic rhinitis preoperatively. Recurrence of OSAS from 6 to 36 months after adenotonsillectomy was significantly associated with persistent enuresis, age, AHI at 6 months postoperatively, and the rate of change in body mass index and body weight.
Hsu et al, 2013 [171]	Retrospective, cohort study	IV	161 children (mean age, 7.0 ± 3.4 years; 78% boys) with OSAS who underwent adenotonsillectomy.	All patients had polysomnography before and after surgery. Children were classified into underweight, normal weight, overweight and obese, based on age and gender corrected body mass index. Postoperatively, all four groups significantly improved regarding AHI and SpO_2 nadir. 49.1% of all children (79/161) had residual OSAS (AHI ≥ 1 episode/h). The incidence of residual OSAS in the obese group was 75%, which was significantly higher compared to the other three groups (P<0.01). 54% (13/24) of the underweight children attained normal weight status within 6 months after surgery.
Marcus et al, 2013 [192]	Randomized controlled multicentre trial early adenotonsillectomy versus watchful waiting	I	464 (5-9 y.o.), 46% children in the watchful waiting group and 48% in the early treatment group were overweight or obese	33% of obese and 15% of nonobese children in the early adenotonsillectomy group vs. 71% of obese and 46% of nonobese in the watchful waiting group had residual OSAS (AHI >2 episodes/h or obstructive apnea index > 1 episode/h) at 7 months follow-up. Children with preoperative AHI >4.7 episodes/h were significantly more likely to have residual OSAS than subjects with lower preoperative AHI.
Nandalike et al, 2013 [305]	Prospective, cohort study		27 obese children with OSAS (age 13.0 ± 2.3 years; body mass index Z-score	Polysomnography and magnetic resonance imaging of the head including

			2.5 ± 0.3) who underwent adenotonsillectomy	the upper airway during wakefulness before and 6.1 ± 3.6 months after adenotonsillectomy were performed. The mean obstructive AHI decreased from 23.7 ± 21.4 episodes/h to 5.6 ± 8.7 episodes/h (P < 0.001). OSAS resolution was noted in 44% (12 of 27) children, but only in 22% (4 of 18) of those patients with severe OSAS (AHI > 10 episodes/h). Following adenotonsillectomy the volume of the nasopharynx and oropharynx increased significantly (P < 0.001 and P < 0.01, respectively) and the volume of tonsils reduced significantly (P < 0.001). However, there was no change in the volume of the adenoid, lingual tonsil, or retropharyngeal nodes. The volume of the soft palate and tongue increased significantly (P = 0.02 and P = 0.005, respectively).
Nath et al, 2013 [306]	Retrospective cohort study	IV	283 patients (mean age, 22 ± 7 months) underwent preoperative polysomnography and 70 of them had also postoperative polysomnography.	In the group with both preoperative and postoperative polysomnography, there were statistically significant improvements in AHI (from 34.8 ± 40.7 to 5.7 ± 13.8; P < .001) baseline oxygen saturation (from 96.6% ± 2.1% to 97.2% ± 1.4%; P = .05), minimum oxygen saturation (from 77.2% ± 11.4% to 89.9% ± 6.8%; P < .001), and sleep efficiency (from 84.7% ± 14.9% to 88.7% ± 9.1%; P = .02) after adenotonsillectomy. When AHI >5 was used to define OSAS, 21% of the patients had residual OSAS. The most consistent predictor of residual OSAS postoperatively was the severity of preoperative OSAS (P = .02).
Zandieh et al, 2013 [270]	Retrospective, cohort study	IV	47 patients with syndromic craniosynostosis and age <21 years (66 % Apert syndrome; 19 % Pfeiffer syndrome; 15 % Crouzon syndrome).	Mean age of participants at first visit was 1.2 ± 3.3 years and they were followed for a mean of 14.6 ± 8.6 years. Of children with at least 1 sleep study, 83% had OSAS (severe in 42% of cases, moderate in 19% and mild in 22). Adenotonsillectomy was performed in 62% of patients and preoperative and postoperative polysomnography was carried out in 45% of them. Postoperatively, the mean AHI did not change significantly and OSAS persisted persisted in 11 of 13 patients.

Tagaya et al, 2012 [307]	Prospective, cohort study	IV	49 normal-weight children (1-10 y.o.) with severe or moderate OSAS (AHI ≥5 episodes/h) who underwent adenotonsillectomy.	Polysomnography was performed before adenotonsillectomy, at 2–4 months postoperatively and at 1.5 year postoperatively for children who had recurrent symptoms of SDB. Nasal endoscopy was carried out every 3 months for 1.5 years after surgery. At 1.5 years after adenotonsillectomy, 13 of 49 children had symptoms of SDB with episodes of apnea, recurrent snoring or nasal Allergic rhinitis (38.5% vs 11.1%; P = 0.03) and allergic disease (69.2% vs 30.6%; P = 0.02) were more frequent in children with recurrent symptoms compared to those who remained asymptomatic. 9 of 13 children had AHI ≥5 episodes/h and 6 children (12.2% of all children) had adenoid regrowth and three (6.1%) underwent revision adenoidectomy.
Bhattacharjee et al, 2010 [220]	Retrospective, multicenter study	IV	578 (mean age, 6.9 ± 3.8 years), 50.6% of subjects were obese	Age and body mass index z-score were the two principal predictors of postoperative AHI. Presence of asthma and magnitude of preoperative AHI were less important predictors among nonobese children.
Costa et al, 2009 [308]	Meta-analysis	-	4 studies including 110 obese children (range of sample size 18-33 subjects).	The mean body mass index z-score was 2.81 and the mean pre- and postoperative AHI was 29.4 (22.2-34.3) and 10.3 (6.0-12.2) episodes/h, respectively. 12% had a postoperative AHI< 1 episodes/h and 49% had a postoperative AHI <5 episodes/h.
Apostolidou et al, 2008 [309]	Retrospective cohort study	III	22 obese and 48 nonobese subjects without significant differences in preoperative polysomnography indices and size of adenoid/tonsils	22.7% of obese and 25% of nonobese subjects had a postoperative obstructive AHI < 1 episode/h. This difference was not significant.
Guilleminault et al, 2007 [310]	Prospective cohort without concealed allocation to subgroups	IV	207 successively seen children (7.3 ± 2.3 y.o.) underwent adenotonsillectomy, 199 had follow-up polysomnography	94 subjects had OSAS postoperatively. Mallampati scale score 3 and 4, retro-position of mandible, enlargement of nasal inferior turbinates, and deviated nasal septum were significantly associated with persistent OSAS (AHI>1 episode/h).
Amonoo-Kuofi K et al, 2009 [271]	Retrospective case series	IV	26 with syndromic craniosynostosis and	Seven subjects had severe OSAS, 11 had

			mean age 4.5 years (range, 1.6-13.9 y	moderate OSAS, and 7 had mild OSAS prior to adenotonsillectomy. 60% demonstrated improvement in sleep severity score postoperatively.
Merrell et al, 2007 [285]	Retrospective cohort study	III	Down syndrome, 21 treated by adenotonsillectomy, 16 underwent adenotonsillectomy plus lateral pharyngoplasty	52% of patients in the adenotonsillectomy alone group had a normal AHI postoperatively. In the adenotonsillectomy plus lateral pharyngoplasty group, 37% had a normal AHI. Thus, after adenotonsillectomy, an appreciable proportion of subjects will have an abnormal postoperative sleep study. Adding a lateral pharyngoplasty does not improve these results.
Shete et al, 2010 [311]	Retrospective cohort study	III	11 children with Down syndrome (mean age 101 months) and 9 subjects without Down syndrome (mean age 80 months)	In children with Down syndrome a significant decrease in AHI was observed: 15.3 ± 12.6/hr to 9.14 ± 10.5 (p=0.04); only 18% had a postoperative AHI< 2 episodes/h. In the control group 55% had a postoperative AHI<2 episodes/h. REM-AHI and lowest SpO_2 did not improve in subjects with Down syndrome and 73% of them required CPAP, BiPAP or oxygen for persistent OSA after adenotonsillectomy.
Sisk et al, 1999 [53]	Retrospective, cohort study	IV	95 children with achondroplasia and 36 of them with OSAS.	Thirty-four patients underwent surgery, with more than one procedure required in 10 children (29%). Adenotonsillectomy was the initial procedure for 22 of 34 patients, and further therapy for recurrent OSAS was required for 18% of subjects. Adenoidectomy was the initial procedure for 10 of 34, with 90% requiring further surgery for recurrent OSAS. Tonsillectomy alone was performed in 2 patients: 1 was effectively treated and 1 later required adenoidectomy. Thus, recurrent symptoms are common, especially when the initial procedure is adenoidectomy.
Magardino & Tom, 1999 [275]	Retrospective case series	IV	27 children with cerebral palsy	84% had symptomatic improvement with tonsillectomy, adenoidectomy and/or uvulectomy and tracheostomy was avoided. Long-term outcomes were based on parental reports.
Kerschner et al, 2002 [274]	Retrospective case-series	IV	15 children with neurological impairment and OSAS	Treatment consisted of adenotonsillectomy and uvulopalatopharyngoplasty. Primary area

				of obstruction in the posterior oropharynx (soft palate, pharyngeal walls and base of tongue). Pre-postoperative oximetry (n=13) showed significant improvement in mean lowest oxygen saturation from 65% preoperative to 85% postoperative (P=0.005). In long-term follow-up (5.2 years), 77% (10 of 13) of those showing initial improvement did not require additional airway intervention.
Pavone et al, 2006 [312]	Retrospective case-series	IV	5 children with Prader- Willi syndrome and median age 4.4 years (1.6-14.2 years)	Significant improvement in AHI from 12.2 (9.0-19.9) to 1.6 (0.6-4.7) episodes/h, (P=0.009) on cardiorespiratory sleep study following adenotonsillectomy.
c. *Effects of adenotonsillectomy on: i) quality of life; ii) somatic growth rate; iii) frequency of enuresis; iv) pulmonary hypertension and cor pulmonale; and v) morbidity from the central nervous system*				
Author, year	**Type of Study**	**Class**	**Subjects**	**Methods and findings**
i) quality of life				
Garetz et al, 2015 [173]	Multicentre, single-blind, randomised, controlled trial	I	464 children (5-9 y.o.) with OSAS randomly assigned to early adenotonsillectomy (median baseline obstructive AHI 4.8 episodes/h) or watchful waiting (median baseline obstructive AHI 4.5 episodes/h). OSAS was defined as an obstructive AHI ≥2 episodes/h or an obstructive apnea index ≥1 episode/h. The Pediatric Quality of Life inventory, the Sleep-Related Breathing Scale of the Pediatric Sleep Questionnaire, the 18-item Obstructive Sleep Apnoea QoL instrument, and the modified Epworth Sleepiness Scale were completed before adenotonsillectomy and at 7 months postoperatively.	Greater improvements regarding most measures of quality of life and symptom severity were demonstrated in the early adenotonsillectomy group than in the watchful waiting arm. There was weak correlation between improvement in polysomnography indices and changes in quality of life or symptom severity measures. Baseline OSAS severity did not influence the association between quality of life or symptom severity measures and treatment arm.
Lee et al, 2014 [313]	Prospective, cohort study	III	144 children with SDB symptoms (mean age 7.0 ± 3.6 years; range 2-18 years; 76% boys).	Prior to adenotonsillectomy, all children underwent polysomnography and caregivers completed the OSA-18 quality of life questionnaire. A follow-up OSA-18 questionnaire was completed within 3 months after adenotonsillectomy. Disease severity was classified as: primary snoring (AHI <1 episode/h); mild OSAS (5> AHI ≥1 episodes/), and moderate-to-severe OSAS (AHI ≥5 episodes/h). Children with moderate-to-severe OSAS had greater improvement in OSA-18 postoperatively than participants with mild OSAS or primary snoring.

Volsky et al, 2014 [266]	Prospective, cohort study	III	64 children (3-16 y.o.) with mild OSAS (AHI 1-5 episodes/h); 30 patients chose adenotonsillectomy, and 34 chose observation.	At baseline, early and late follow-up visits, caregivers completed two validated quality-of-life instruments (OSA-18 and Children's Health Questionnaire). At baseline, children in the adenotonsillectomy group had significantly poorer total OSA-18 scores than those in the observation group (72.3 vs. 58.5; P=0.01). At 4 months after surgery, OSA-18 scores improved by 39.1 points compared to baseline (P = 0.0001), but there was no change in the observation group (P >0.05). At 8 months postoperatively, OSA-18 scores remained improved in the surgery group but there was no statistically significant difference compared to the observation group (P=0.05).
Marcus et al, 2013 [192]	Multicenter, single-blind, randomized, controlled trial	I	464 children (5-9 y.o.) with OSAS randomly assigned to early adenotonsillectomy (median baseline obstructive AHI 4.8 episodes/h) or watchful waiting (median baseline obstructive AHI 4.5 episodes/h)	Quality of life (Pediatric Quality of Life Inventory, PedsQL and the OSA-18 score) and polysomnography were assessed at baseline and at 7 months. AHI normalized in significantly more children in the early-adenotonsillectomy group than in the watchful-waiting group (79% vs. 46%; P<0.01). The early-adenotonsillectomy group had significantly greater improvement in quality of life (PedsQL and OSA-18) than the watchful-waiting group.
Randhawa et al, 2011 [268]	Prospective, cohort study	III	4-year follow-up study of 33 children (mean age 10.6 years; median 11 years; range 5-16 years) who underwent adenotonsillectomy for OSAS (18 girls) and of 221 healthy controls (6-18 y.o.).	The Child Health Questionnaire Parental Form version-28 was completed 4 years after adenotonsillectomy. When compared to data at 3 months postoperatively, the mean scores were higher in five domains and statistically significant in three subscales (Role Limitations; P < 0.00001; Bodily Pain; P < 0.002; and Global Health P < 0.02). There was a significant deterioration in Behaviour subscale (P < 0.0007). Compared with controls, at the 4-year follow-up, scores were higher in five domains with statistically significant difference in the Global Health domain (P < 0.0004). Improvements after adenotonsillectomy persisted 4 years postoperatively.
Baldassari et al, 2008 [174]	Meta-analysis	-	10 studies including 1470 children: 562	In three studies, 193 patients with OSAS,

			children with OSAS, 815 healthy children, and 93 children with juvenile rheumatoid arthritis	93 children with juvenile rheumatoid arthritis and with 815 healthy children were compared using the Child Health Questionnaire (CHQ). Children with OSAS had poorer scores in 8 of 12 CHQ subscale scores than controls. Children with OSAS had poorer scores in the parental impact-emotional subscale than healthy controls. Children with OSAS were similar to patients with juvenile rheumatoid arthritis regarding quality of life scores. In seven studies, 369 children with OSAS underwent adenotonsillectomy and the OSA-18 total and subscale scores improved significantly ($P < 0.0001$). Improvement persisted at long-term follow-up.
Garetz et al, 2008 [259]	Systematic review	-	25 articles with sample sizes of 19 to 297 subjects with SDB who underwent adenotonsillectomy; 10 studies evaluated postoperative changes in quality of life, 4 studies changes in behavior, and 3 studies in neurocognitive skills; 5 studies evaluated changes in behavior and cognition, and 2 studies examined improvements in behavior and quality of life; 1 study evaluated changes in cognition, behavior, and quality of life.	All studies demonstrated improvements in quality of life, behavioral problems (including hyperactivity and aggression), and neurocognitive skills (memory, attention, or school performance). There is poor correlation between improvements in outcome measures and polysomnographic variables.
ii) somatic growth rate				
Katz et al, 2014 [264]	Multicentre, single-blind, randomised, controlled trial	I	464 children (5-9 y.o.) with OSAS randomly assigned to early adenotonsillectomy (median baseline obstructive AHI 4.8 episodes/h) or watchful waiting (median baseline obstructive AHI 4.5 episodes/h) and were followed for 7 months. OSAS was defined as an obstructive AHI ≥2 episodes/h or an obstructive apnea index ≥1 episode/h.	Polysomnography and measurement of weight and height were performed at baseline and 7-month follow-up. Multivariable regression modeling was used to predict the change in weight and growth indices. During the observation period body mass index z-score increased in both arms, but it was greater in the early adenotonsillectomy ($P < 0.0001$). A greater proportion of overweight children in the early adenotonsillectomy group became obese during the 7-month observation period compared to participants in the watchful waiting group (52% vs. 21%; $P < 0.05$). Baseline AHI was positively associated with the postoperative body mass index z- score change.

Hsu et al, 2013 [171]	Retrospective, cohort study	IV	161 children (mean age, 7.0 ± 3.4 years; 78% boys) with OSAS who underwent adenotonsillectomy.	All patients had polysomnography before and after surgery. Children were classified into underweight, normal weight, overweight and obese, based on age and gender corrected body mass index. Postoperatively, all four groups significantly improved regarding AHI and SpO_2 nadir. 49.1% of all children (79/161) had residual OSAS (AHI ≥ 1 episode/h). The incidence of residual OSAS in the obese group was 75%, which was significantly higher compared to the other three groups (P<0.01). 54% (13/24) of the underweight children attained normal weight status within 6 months after surgery.
Smith et al, 2013 [314]	Retrospective, cohort study	IV	115 children who underwent adenotonsillectomy for OSAS (n=85; mean age 7.2 ± 4.3 years) or recurrent tonsillitis (n=30; mean age 7.3 ± 4.4 years)	The BMI z-score prior to adenotonsillectomy increased (from 0.98 ± 1.50 to 1.21 ± 1.25; P = 0.0009) regardless of the surgical indication. On multivariable analysis age was significantly, and negatively associated with changes in BMI z-score (P = .015).
Bonuck et al, 2009 [172]	Systematic review and meta-analysis	-	20 studies analyzed (ages 5 months-15.8 years); a total of 363 children were evaluated for height change post-adenotonsillectomy and 390 subjects for weight change	Over a follow-up period ranging from 1 month to 3 years, the pooled standardised mean increase in height (z score) postoperatively was 0.34 (95% CI 0.20-0.47) and in weight 0.57 (95% CI 0.44-0.70).
iii) enuresis				
Kovacevic et al, 2014 [261]	Prospective, cohort study	IV	46 children (5-18 y.o.)with snoring or OSAS and monosymptomatic primary nocturnal enuresiswho underwent adenotonsillectomy for release of upper airway obstruction	Plasma antidiuretic hormone and brain natriuretic peptide were measured preoperatively and 1 month postoperatively. 32 children underwent blood testing preoperatively and postoperatively. The mean number of wet nights weekly was 6.39 ± 1.26. Polysomnography revealed OSAS in 71.7% of patients and snoring in 28.3%. After adenotonsillectomy 43.5% of patients became dry. Children who became dry postoperatively had significantly more arousals and obstructive apnea episodes but fewer awakenings than nonresponders, who remained wet. Significant increases in plasma antidiuretic hormone and decreases in plasma brain natriuretic peptide levels were demonstrated in all

				children irrespective from resolution of enuresis.
Jeyakumar et al, 2012 [164]	Systematic review	-	Pediatric studies from 1980 to 2010 on the association of SDB with enuresis and the effects of adenotonsillectomy were reviewed. 14 studies were reviewed including 3,550 children (age 18 months-19 years) with SDB, of whom one-third (n = 1,113) had a diagnosis of enuresis; in 7 studies (n =1,360) frequency of enuresis was evaluated also post-adenotonsillectomy (median follow-up of 6 months; age range of 2-18 years).	Preoperative prevalence of enuresis was 31% and postoperative prevalence was 16% (P = 0.002). Most studies did not separate primary from secondary enuresis. Some subjects probably had age-appropriate enuresis.
iv) pulmonary hypertension, cor pulmonale and increased heart rate				
Quante et al, 2014 [106]	Multicentre, single-blind, randomised, controlled trial	I	464 children (5-9 y.o.) with OSAS randomly assigned to early adenotonsillectomy (median baseline obstructive AHI 4.8 episodes/h) or watchful waiting (median baseline obstructive AHI 4.5 episodes/h). OSAS was defined as an obstructive AHI ≥2 episodes/h or an obstructive apnea index ≥1 episode/h.	There was a positive association between nocturnal heart rate and baseline OSAS severity (average heart rate increase of 3 beats per minute for AHI of 2 versus 10 episodes/h. For each 5-unit improvement in AHI and 5 mmHg improvement in peak end-tidal CO2 there was a reduction in heart rate by 1 and 1.5 beats per minute, respectively.
Martha et al, 2013 [254]	Prospective, cohort study	IV	33 children (1-12 y.o.) with adenotonsillar hypertrophy and snoring or oral breathing without genetic syndromes, neuromuscular disorders or craniofacial abnormalities; 10 healthy control chidlren.	Participants underwent echocardiography before and 2-24 weeks after adenoidectomy or adenotonsillectomy. Pulmonary hypertension (mean pulmonary artery pressure ≥25 mmHg) was identified in 12 (36%) of the 33 children with adenotonsillar hypertrophy. In children with pulmonary arterial hypertension, adenoidectomy or adenotonsillectomy were accompanied by a significant decrease in mean pulmonary arterial pressure (from 27 ± 2.8 to 20 ± 5.1 mmHg; P<0.001) and by a non-significant decrease in systolic pulmonary arterial pressure (from 35 ± 6.2 mmHg to 25 ± 0.5 mmHg, P=0.243). The pulmonary arterial values in children without pulmonary hypertension did not change postoeratively.
Miman et al, 2000 [113]	Retrospective, cohort study	IV	17 children (20-96 months old) with adenotonsillar hypertrophy, SDB and pulmonary hypertension	Pulmonary arterial pressure was measured by Doppler echocardiography. Following adenoidectomy and/or tonsillectomy mean preoperative pulmonary arterial pressure decreased from 29.12 ± 4.41 mmHg to 12.06 ± 3.09 mmHg (P<0.01). Upper respiratory

				obstruction symptom score also decreased significantly postoperatively (P<0. 01) in the postoperative period.
Tal et al, 1988 [315]	Prospective, cohort study	IV	27 children with oropharyngeal obstruction and clinical manifestations of OSAS (mean age 3.5 years; range: 9 months-7.5 years).	Children underwent radionuclide ventriculography prior to adenotonsillectomy. Reduced right ventricular ejection fraction (<35%) was demonstrated in 10 (37%) children (mean 19.5%; range: 8-28%). There was wall motion abnormality in 18 patients. In 11 children, radionuclide ventriculography was repeated postoperatively and right ventricular ejection fraction increased from 24.4 ± 3.6% to 46.7 ± 3.4% (P <0.005); in all subjects wall motion improved. In 5 children, left ventricular ejection fraction increased >10% postoperatively.
v) morbidity from the central nervous system				
Rosen et al, 2015 [246]	Multicenter, single-blind, randomized, controlled trial	I	464 children (5-9 y.o.) with OSAS randomly assigned to early adenotonsillectomy (median baseline obstructive AHI 4.8 episodes/h) or watchful waiting (median baseline obstructive AHI 4.5 episodes/h). Baseline and 7-month follow-up data were analysed from 185 children in the early adenotonsillectomy arm. Associations were assessed between baseline Pediatric Sleep Questionnaire score or AHI and postoperative changes in the NEPSY and executive function, behavior, quality of life and sleepiness as rated by parents.	Higher baseline Pediatric Sleep Questionnaire scores-but not the baseline AHI- predicted postadenotonsillectomy improvement in executive functioning, behavior, quality of life, and sleepiness as rated by parents. Neither the Pediatric Sleep Questionnaire nor polysomnographic parameters were associated with objectively assessed executive dysfunction (NEPSY score) or its improvement postoperatively.
Sedky et al, 2014 [131]	Meta-analysis	-	*Relationship between SDB and attention-deficit, hyperactivity disorder symptomatology:* 18 studies with 1113 children in the clinical group (874 had SDB and were examined for attention-deficit, hyperactivity disorder symptoms; 239 had attention-deficit, hyperactivity disorder and were examined for SDB) and 1405 in the control group. *Difference between attention-deficit, hyperactivity disorder symptomatology pre- versus post-adenotonsillectomy:* 12 studies (529 subjects) were identified assessing pre- versus post-surgery	*Relationship between SDB and attention-deficit, hyperactivity symptomatology:* Medium relationship was demonstrated between attention-deficit, hyperactivity symptoms and SDB (Hedges' g=0.57, 95% CI 0.36-0.78; p< 0.001). A high AHI cutoff was associated with lower effect sizes, while child age, gender and BMI did not moderate the relationship between SDB and attention-deficit, hyperactivity disorder. Better study quality was associated with larger effect sizes. *Difference between attention-deficit, hyperactivity disorder symptomatology*

			attention-deficit, hyperactivity disorder symptoms	*pre- versus post-AT:* Hedges' g=0.43 (95% CI 0.30-0.55; p < 0.001) suggesting a medium effect i.e. adenotonsillectomy was associated with decreased attention-deficit, hyperactivity disorder symptoms at 2-13 months postoperatively.
Marcus et al, 2013 [192]	Multicenter, single-blind, randomized, controlled trial	I	464 children (5-9 y.o.) with OSAS randomly assigned to early adenotonsillectomy (median baseline obstructive AHI 4.8 episodes/h) or watchful waiting (median baseline obstructive AHI 4.5 episodes/h)	Polysomnographic, cognitive, behavioral, and health outcomes were assessed at baseline and at 7 months. Average baseline value for the attention and executive-function score on the Developmental Neuropsychological Assessment (primary outcome), was close to the population mean of 100, and the change from baseline to follow-up did not differ significantly between the early-adenotonsillectomy group and the watchful-waiting group; P=0.16). There were significantly greater improvements in behavioral, quality-of-life, and polysomnographic findings and significantly greater reduction in symptoms in the early-adenotonsillectomy group compared to the watchful-waiting group. Normalization of polysomnographic findings was observed in a larger proportion of children in the early-adenotonsillectomy group than in the watchful-waiting group (79% vs. 46%).
Giordani et al, 2012 [142]	Prospective cohort study	II	105 children (5-12 y.o.) with OSAS, primary snoring or controls	At 1 year after adenotonsillectomy there were improvements in polysomnography, sleepiness and parental reports of behavior, with mixed changes in cognitive outcomes. Children undergoing adenotonsillectomy with and without polysomnography-confirmed OSAS improved in academic achievement measures, short-term attention/working memory, executive functioning, and parental ratings of behavior. Measures of verbal abstraction ability, arithmetic calculations, visual and verbal learning, verbal delayed recall, sustained attention demonstrated declines.
Kohler et al, 2010 [258]	Systematic review	-	Only studies with SDB diagnosed by polysomnography were included (published till November 2009): 27 adenotonsillectomy studies; 2	Most studies were focused on children of school age and the follow-up data period was less than a year. In many studies, no postoperative polysomnography was

			tracheostomy studies; 1 study with unspecified surgery and continuous positive airway pressure	performed and control subjects were not evaluated at two time points. Overall, improvement was demonstrated in global intelligence, attention, and visual–spatial ability, but deficits in language and short-term memory appeared to persist. Hyperactivity, aggression and conduct problems and somatic complaints also improved postoperatively. However, symptoms of anxiety and social problems did not seem to improve. Abnormalities at baseline evaluation were not clinically apparent.
Garetz et al, 2008 [259]	Systematic review	-	25 articles with sample sizes of 19 to 297 subjects with SDB who underwent adenotonsillectomy; 17 of the studies evaluated a single outcome variable after surgical intervention; 10 studies evaluated postoperative changes in quality of life, 4 studies changes in behavior, and 3 studies in neurocognitive skills; 5 studies evaluated changes in behavior and cognition, and 2 studies examined improvements in behavior and quality of life; 1 study evaluated changes in cognition, behavior, and quality of life.	All studies demonstrated improvements in quality of life, behavioral problems (including hyperactivity and aggression), and neurocognitive skills (memory, attention, or school performance). There is poor correlation between improvements in outcome measures and polysomnographic variables.
Chervin et al, 2006 [260]	Prospective cohort study	II	105 children (5-12.9 y.o.): 78 scheduled for clinically indicated adenotonsillectomy, usually for SDB, and 27 for unrelated surgical care	Subjects undergoing adenotonsillectomy for suspected SDB, as compared to controls, were more hyperactive on parent rating scales, inattentive on cognitive testing, more sleepy on the Multiple Sleep Latency Test, and more likely to have attention-deficit/hyperactivity disorder as judged by a child psychiatrist. At 1 year follow-up, the 2 groups showed no significant differences in the same measures. Subjects who underwent adenotonsillectomy improved in all measures, and control subjects improved in none. Polysomnographic indices at baseline and at follow-up did not predict baseline neurobehavioral morbidity or improvement in any area other than sleepiness.

d. *Complications of adenotonsillectomy*				
Author, year	**Type of Study**	**Class**	**Subjects**	**Findings**
Konstantinopoulou et al, 2015 [214]	Multicenter, single-blind, randomized, controlled trial	I	464 children (5-9 y.o.) with OSAS and without comorbidities except for obesity or asthma were randomly assigned to early adenotonsillectomy (median baseline obstructive AHI 4.8 episodes/h) or watchful waiting (median baseline obstructive AHI 4.5 episodes/h). OSAS was defined as an obstructive AHI ≥2 episodes/h or an obstructive apnea index ≥1 episode/h.	Data from 221 children who underwent adenotonsillectomy were analysed. Associations between demographic variables and surgical complications were explored. Subjects with and without postadenotonsillectomy complications were compared regarding polysomnography variables. Preoperative AHI was 2-30 episodes/h and obstructive apnea index was 1.2-27.7 episodes/h and 31% of children were obese. 16 (7%) children had postoperative complications. 3 (1.4%) children had respiratory complications (pulmonary edema, hypoxemia and bronchospasm); 13 patients (5.9%) had non-respiratory complications (dehydration-4.5%; hemorrhage-2.3%; and fever-0.5%). There were no significant associations between gender, race, and obesity or polysomnographic parameters (AHI, % total sleep time with SpO_2<92%, SpO_2 nadir, % sleep time with end-tidal CO_2>50 mmHg) and presence of complications.
Lee et al, 2013 [230]	Retrospective cohort study	III	231 children (≥ 3 y.o.) who underwent adenotonsillectomy and had a McGill oximetry score of 1 on home nocturnal oximetry	None of the patients had a major postoperative respiratory complication requiring re-intubation or hospital admission. 2.16% of patients had minor respiratory complications.
Jaryszak et al, 2011 [216]	Retrospective cohort study	III	1131 patients undergoing adenotonsillectomy; 151 patients (13.4%) underwent preoperative polysomnography	23 patients (15.2%) had adverse respiratory events. The primary adverse event was desaturation requiring supplemental oxygen therapy, with 1 case of post-obstructive pulmonary edema. Patients with adverse events had a significantly higher AHI (31.8 vs 14.1 episodes/h; P = 0.001), higher body mass index (z score, 1.43 vs 0.70; P = 0.02), and lower nadir SpO_2 (72% vs 84%; P <0.001). Patients with adverse events had a prolonged hospital course (OR 32.1; 95% CI 7.8-131.4).
Fung et al, 2010 [316]	Prospective cohort study	III	49 obese children with OSAS versus 49 nonobese children with OSAS matched for age and gender	Obese children had significantly more overall complications compared with controls (OR 8.54; 95% CI 3.44-21.19). Obese children had higher frequency of upper airway obstruction (OR 7.13; 95%

				CI 2.20-23.03) during the immediate postoperative period. Mean hospital stay was significantly longer for the obese group (mean difference of 10 hours; 95% CI 2.01-17.99).
Ye et al, 2009 [217]	Retrospective, cohort study	IV	Four hundred seventy-five consecutive cases for adenotonsillectomy were identified, and 321 children (4-14 y.o.) were included (AHI ≥5 episodes/h).	Demographic data, history, preoperative sleep evaluation, surgical and anesthetic management, and need for postoperative respiratory interventions were reviewed. 36 children (11.2%) had postoperative respiratory complications requiring an intervention. Of the 36, 29 children (80.6%) required an oropharyngeal or nasopharyngeal airway. Twenty-five children (69.4%) experienced multiple episodes of desaturation, and 61.1% of cases had respiratory complications in the postanesthesia care unit. Young age, obesity, and high preoperative AHI were risk factors for postoperative respiratory complications. More specifically, an AHI >26 episodes/h had 74% sensitivity and 92% specificity for predicting postoperative respiratory complications.
Sanders et al, 2006 [317]	Prospective cohort study	III	61 children with OSAS and 21 with recurrent tonsillitis (ages 2-16 years) undergoing adenotonsillectomy	Children with OSAS had significantly more respiratory complications (supraglottic obstruction, breath holding, and desaturation on anesthetic induction and emergence) per operation (5.7) compared to non-OSAS children (2.9); $p < 0.0001$. Increased OSAS severity, low weight, and young age were correlated with increased rate of complications. Both groups of children had similar opioid requirements and time to discharge from the recovery room.
Nixon et al, 2004 [218]	Prospective cohort study Phase 1: Development of oximetry score Phase 2: Retrospective validation of the score Phase 3: Prospective evaluation of the score	II	Phase 3: 230 children (median age 4.3 years) underwent nocturnal oximetry at home for suspected OSAS.	113 children underwent adenotonsillectomy and information on the postoperative course was available for 109 subjects. Oximetry was positive (at least 3 drops in SpO_2 to less than 90% and at least 3 clusters of desaturation (≤ 4%) events) in 22% of cases and detected 25 of 35 (sensitivity 71%) of those who required any intervention for postoperative respiratory compromise and 6 of 7 (sensitivity 86%) of those who had major postoperative respiratory

				compromise.
Wilson et al, 2002 [219]	Retrospective cohort study	IV	163	A preoperative AHI >5 episodes/h increased the risk for postopartive respiratory complications (OR 7.2; 95% CI 2.7-19.3). 34 children (21%) had postoperative respiratory complications requiring a medical intervention. Children with respiratory complications were younger (aged < 2 yr; adjusted OR 4.3; 95% CI 1.7-11) and had an associated medical condition (OR 3; 95% CI 1.4-6.5). A preoperative obstructive AHI ≥ 5 episodes/h increased the chance of postoperative respiratory complications (OR 7.2; 95% CI 2.7-19.3); also a preoperative oxygen saturation nadir ≤ 80% (OR 6.4; 95% CI 2.8-14.5).
Biavati et al, 1997 [318]	Retrospective, cohort study	IV	355 children who underwent adenotonsillectomy for SDB	Frequency of postoperative complications (airway obstruction, apneas with oxygen desaturations, endotracheal intubation, administration of supplemental oxygen) was related to accompanying medical conditions (cerebral palsy, seizures, age ≤3 years, congenital heart disease or prematurity) and findings of diagnostic tests (e.g., chest x-ray film and electrocardiogram). All 5 medical conditions were significant predictors of a complicated postoperative course using stepwise logistic regression analysis. Also abnormal chest x-ray film or electrocardiogram corresponded to an associated medical condition that was predictive of postoperative complications. More specifically, the odds ratio for postoperative respiratory complications was 6.8 in children with cerebral palsy (95% CI 0.97-47.2) and 5.2 in children with epilepsy (95% CI 1.2-22.6) compared to subjects without such conditions. An abnormal preoperative polysomnogram had a 63% predictive value for a complicated postoperative course while a normal preoperative polysomnogram predicted an uncomplicated postoperative course.

e. *Efficacy of intranasal corticosteroid and oral montelukast or myofunctional re-education for persistent OSAS after adenotonsillectomy*				
Villa et al, 2015 [319]	Prospective, cohort study	III	Children with an AHI >1 episode/h after adenotonsillectomy for OSAS were recruited. Group 1 included 14 subjects (mean age 6.01 ± 1.55 years); group 2 included 13 subjects (mean age 5.76 ± 0.82 years). The AHI was 16.79 ± 9.34 episodes/h before adenotonsillectomy and 4.72 ± 3.04 episodes/h at 6 months postoperatively.	Group 1 subjects were treated with oropharyngeal exercises and daily nasal washings whereas group 2 particpants received only daily nasal washings. After 2 months of the intervention polysomnography was repeated. The % reduction in the AHI was significantly higher in group 1 (58.01%; range 40.51 to 75.51%) than in group 2 (6.96%; range -23.04 to 36.96%).
Guilleminault et al, 2013 [320]	Retrospective, cohort study	IV	24 children (3.6-6.6 y.o.) who underwent adenotonsillectomy and orthodontic treatment for residual OSAS were classified into those receiving myofunctional re-education (n=11) and those not receiving such re-education (n=13).	Participants had repeat polysomnography 22-50 months after the myofunctional re-education or orthodontic treatment. Subjects who did not receive myofunctional reeducation developed recurrence of symptoms with a mean AHI 5.3 ± 1.5 episodes/h and mean SpO_2 nadir 91 ± 1.8%. All 11 subjects who completed myofunctional reeducation for 24 months had normal polysomnography results at follow-up evaluation (mean AHI 0.5 ± 0.4 episodes/h; mean and mean SpO_2 nadir 96 ± 1%).
Kheirandish et al, 2006 [321]	Retrospective cohort study	IV	Children who underwent adenotonsillectomy for SDB and had AHI >1 and <5 episodes/h 10-14 weeks postoperatively; 22 subjects received intranasal budesonide and oral montelukast for 12 weeks and 14 children served as control subjects.	Mean AHI postoperatively was 3.9 ± 1.2 episodes/h in treated children and 3.6 ± 1.4 episodes/h in controls. The treated group demonstrated significant improvements in AHI (0.3 ± 0.3 episodes/hour, nadir arterial oxygen saturation, and respiratory arousal index, whereas no significant changes were found in control subjects.

Question 6.5. Is adenotonsillectomy more efficacious than adenoidectomy or tonsillectomy alone in terms of decreasing severity of obstructive SDB?				
Author, year	**Type of Study**	**Class**	**Subjects**	**Methods and findings**
Wood et al, 2014 [322]	Systematic review	-	18 studies were reviewed assessing subototal tonsillectomy for SDB	Subtotal tonsillectomy seems to have similar efficacy to that of total tonsillectomy for the treatment of SDB, it is associated with reduced postoperative pain and analgesia use and less frequent postoperative haemorrhage compared to total tonsillectomy.
Chaidas et al, 2013 [323]	Prospective, cohort study	III	51 children with SDB (mean age 6.3 ± 2.5 years) underwent partial	Children with SDB were followed during the immediate postoperative

			tonsillectomy; 50 children with SDB (mean age 5.9 ± 2.1 years) had tonsilloplasty.	period and at 6 years after surgery. Children in the tonsilloplasty group had significantly less intraoperative bleeding and less postoperative pain compared to children in the partial tonsillectomy group. Also they returned to a normal diet sooner. By the 3rd to 4th postoperative night, SDB symptoms resolved in all children. 6 years after surgery, 48 of 51 children in the partial tonsillectomy group and 43 of 50 children in the tonsilloplasty group participated in a telephone survey. There were no differences between the two groups regarding the frequency of recurrent snoring (30.2% with tonsilloplasty vs. 25% with partial tonsillectomy), apneas (4.7% vs. 0%), and upper airway infections per year (P > 0.05).
Kay et al, 2005 [324]	Retrospective cohort study and nested case-control study	III	2462 patients (5 months- 18 years old) underwent adenoidectomy	During 5.4 years of follow-up, 108 patients underwent subsequent tonsillectomy. The overall incidence rate for tonsillectomy was 2%. Of the 196 patients in the nested case-control study, 102 underwent a subsequent tonsillectomy. The relative risk of subsequent tonsillectomy decreases by 0.83 (95% confidence interval, 0.78-0.88) for each increasing year of age at adenoidectomy. The odds of undergoing a future tonsillectomy significantly increase with increasing tonsil size at the time of adenoidectomy.

Question 6.6. What are the indications, efficacy and potential complications of rapid maxillary advancement and orthodontic appliances?				
a+b. *Indications, efficacy and complications of rapid maxillary advancement and orthodontic appliances*				
Author, year	**Type of Study**	**Class**	**Subjects**	**Methods and findings**
Katyal et al, 2013 [267]	Prospective, cohort study	IV	81 children (age 8-17 years) recruited from an orthodontic clinic	Participants were classified as low risk or high risk for OSAS based on results of the OSA-18 questionnaire. All children underwent cephalometric assessment and dental cast analysis at baseline. 10 children who had rapid maxillary expansion were followed longitudinally until removal of the appliance (approximately 9 months). Frequency of palatal crossbite (at least 3

				teeth) was significantly higher in the high-risk group than in the low-risk group at 68.2% vs. 23.2%; P <0.0001). Mean inferior airway space, posterior nasal spine to adenoidal mass distance, and adenoidal mass to soft palate distance were decreased in the high-risk group compared with the low-risk group (P<0.05). Also, the mean maxillary intercanine, maxillary interfirst premolar, maxillary interfirst molar, mandibular intercanine, and mandibular interfirst premolar widths were reduced in the high-risk group compared with the low-risk group (P<0.05). Children in the high-risk group who underwent rapid maxillary expansion had an average improvement of 14% in quality of life scores. In contrast, children in the low-risk group, there was a slight worsening in quality of life related to SDB by an average of 1% following rapid maxillary expansion.
Carvalho et al, 2007 [325]	Cochrane review	-	Randomised or quasi-randomised controlled trials comparing oral and functional orthopaedic appliances with placebo or no treatment, in children 15 y.o. or younger.	Primary outcome measure was AHI <1 episode/h. 384 trials were identified but only one study (n=23) fulfilled the inclusion criteria. Results of the study favored the use of oral appliances.
Villa et al, 2007 [326]	Prospective, cohort study	IV	16 patients (6.6 ± 2.0 y.o.) with dental malocclusion, BMI ≤ 85th percentile, and OSAS confirmed by polysomnography	Patients underwent rapid maxillary expansion and were evaluated at baseline and 1 year after the intervention. In 14 subjects who completed the study there was a significant decrease in the AHI (P=0.005) and severity of symptoms.
Cozza et al, 2004 [327]	Prospective, cohort study	IV	20 children with OSAS (10 boys; mean age 5.91 years; range 4 -8 years) and 20 healthy control children (10 boys; mean age 6 years; range 5-7 years).	Children with OSAS underwent polysomnography before and after intervention with a modified monobloc appliance. All children had cephalometric radiographs and study models. Children with OSAS demonstrated a skeletal Class II pattern with reduced mandibular length and a corresponding increase in overbite. The hyoid bone was located superiorly in the OSAS group. 6 months after the intervention in patients with OSAS, there was a significant decrease in AHI and daytime sleepiness and subjective improvement in sleep quality.

Pirelli et al, 2004 [328]	Prospective, cohort study	IV	31 children (mean age 8.7 years) with maxillary contraction, BMI < 24 kg/m^2 and OSAS diagnosed by polysomnography	Rapid maxillary expansion was performed for 10-20 days and maintenance of device and orthodontic treatment for 6-12 months. At baseline, the mean AHI was 12.2 episodes/h. At the 4-month follow-up, all children had AHI < 1 episode/h, the mean cross-sectional expansion of the maxilla was 4.32 ± 0.7 mm and the mean increase of the pyriform opening was 1.3 ± 0.3 mm.
Villa et al, 2002 [329]	Non-blinded, randomized controlled study	III	32 patients (7.1 ± 2.6 y.o.) with OSAS symptoms, malocclusion, and AHI > 1 episode/h.	19 subjects were randomly assigned to a 6-mo trial of an oral appliance and 13 subjects acted as controls. 4 treated subjects and 5 control subjects were lost to follow-up. Polysomnography after the trial showed that treated subjects had significantly lower apnea index (P < 0.001) and hypopnea index values (P < 0.001) than before the trial, whereas in untreated control subjects there was no change.

Question 6.7. What are the indications, efficacy and potential complications of positive airway pressure (CPAP or NPPV) in children with obstructive SDB?				
a+b. *Indications and efficacy of nCPAP or NPPV*				
Author, year	**Type of Study**	**Class**	**Subjects**	**Methods and findings**
Amaddeo et al, 2015 [330]	Prospective, cohort study	IV	26 children (mean age 7.8 ± 6.2 years) with mean CPAP use 10.6 ± 14.4 months and the following diagnoses: Down syndrome; Treacher Collins syndrome; polymalformative syndrome; idiopathic OSAS; achondroplasia; CATCH-22 syndrome; neurofibromatosis type 1 with subglottic neurofibroma; bronchopulmonary dysplasia; Turner syndrome; Menkes syndrome; cherubism; Beckwith-Wiedemann syndrome; pycnodysostosis; Niemann–Pick disease type A; post-intubation laryngeal paralysis; Prader–Willi syndrome.	Polygraphies were performed while on CPAP for 1 month and analyzed using the SomnoNIV Group definitions. 29 polygraphies were analyzed. The index of total respiratory events was low (median value 1.4 episodes/h; range 0-34 episodes/h). The mean number of different types of respiratory events per study was 2±1 (range 0-4), with always a predominant event. Partial or total upper airway obstruction without a decrease in ventilatory drive was the most common event and the most frequently associated with an oxygen desaturation or an autonomic arousal.
Caldarelli et al, 2013 [331]	Prospective, cohort study	IV	39 patients (1-18 years old) who were under long-term NPPV for neuromuscular disease (n= 13), OSAS (n = 15) or lung disease (n = 11) were studied.	Polygraphy was used as a follow-up method to detect respiratory events and associated autonomic arousals or ≥3 % desaturations during nocturnal NPPV. A second polygraphy was performed following adjustment of the NPPV

				settings if a respiratory event occurred >50 times/h. Events recorded during monitoring were: unintentional leaks (27% of patients), patient-ventilator asynchronies (33%), decrease in ventilatory drive (10%), upper airway obstruction with or without reduction in ventilatory drive (11% or 12% of patients respectively). The mean duration of respiratory events was 32 ± 30 % (range 3-96 %) of total recording time. Unintentional leaks were most frequently associated with autonomic arousals, whereas patient-ventilator asynchronies were rarely associated with autonomic arousals or desaturations. 8 children had a second polygraphy and the frequency of the main respiratory event following adjustment of NPPV settings decreased (P = 0.005).
Ramirez et al, 2013 [332]	Retrospective, cohort study	IV	62 children (mean age 10 ± 5 years) with OSAS (n=51) treated with CPAP and neuromuscular disease (n=6) or lung disease (n=5) treated with NPPV.	A sleep study was performed one month after treatment initiation. Mean adherence was 8:17 ± 2:30 h:min per night, and it did not significantly differ between children with CPAP vs. children with NPPV. 72% of the patients used their device >8 h per night. Mean number of nights with CPAP/NPPV use during the last month was 26 ± 5 nights. Treatment adherence was not associated with age, underlying disease, type of interface (nasal, facial mask, or nasal cannula), nocturnal gas exchange, and duration of positive airway pressure treatment. Mean values of nocturnal SpO_2 and transcutaneous CO_2 with CPAP or NPPV were within reference range, except for children with nasal cannula who had 8.1 ± 15.2% of night time a transcutaneous CO_2 level >50 mmHg.
Marcus et al, 2012 [333]	Controlled trial	III	52 children (12 ± 4 y.o.; range 2-16 y.o.; 36 males) diagnosed with: obesity (n=36); genetic syndrome (n=9); central nervous system abnormality (n=6); craniofacial syndrome (n=3); pulmonary disease (n=3); growth hormone deficiency (n=1); Down syndrome (n=6); Prader-Willi syndrome (n=1); cerebral palsy (n=1); autism (n=1);	Children underwent baseline polysomnography followed by a 2-week habituation period at home with CPAP or NPPVand a titration study. At completion of 3-month treatment, polysomnography was repeated on CPAP or NPPV and adherence data were downloaded. Neurobehavioral

			complex chromosomal disorder (n=1).	evaluation was performed at baseline and after 3 months of treatment. Adherence varied widely. Positive airway pressure therapy was associated with significant improvements in attention deficits ($P < 0.001$); sleepiness (Epworth Sleepiness Scale) ($P < 0.001$); behavior ($P < 0.001$); and caregiver- ($P = 0.005$) and child- ($P < 0.001$) reported quality of life. A significant correlation was identified between the decrease in Epworth Sleepiness Scale at 3 months and adherence ($r = 0.411$; $P = 0.006$). Behavioral outcomes improved in the subset of children with developmental delay.
Beebe et al, 2011 [334]	Prospective, cohort study	III	13 overweight children (10-16 y.o.) with OSAS and 15 control overweight children without OSAS.	Positive airway pressure ventilation was prescribed to patients with OSAS; 6 were adherent to positive airway pressure ventilation and 7 were non-adherent. Baseline and follow-up (average 8.6 months) neurocognitive assessments as well as parent and self-reported questionnaires, subject grades and quality of life parameters. In the adherent group (adherence rate of 57%) improvement in self- reported school grades, self-reported school QOL and attention was demonstrated.
McGinley et al, 2009 [335]	Prospective, cohort study	IV	12 children (mean age 10 ± 1 years; Mean body mass index 35 ± 14 kg/m^2), with OSAS (AHI 2-36 episodes/h)	Participants received 20 L/min of air via a nasal cannula. Polysomnography indices were compared at baseline, with the nasal cannula, and on CPAP. Constant airflow decreased the amount of inspiratory flow limitation, the frequency of arousals and the AHI from 11 ± 3 to 5 ± 2 episodes/h ($P < 0.01$). In the majority of children, the decrease in the AHI on the continuous nasal airflow was comparable to that on CPAP.
Uong et al, 2007 [336]	Retrospective, cohort study	IV	46 children (7-19 y.o.; 56% male; mean body mass index 39.8 kg/m^2) with persistent OSAS after adenotonsillectomy.	A polysomnogram was obtained before and after initiation of positive airway pressure therapy. Positive airway pressure was used on average, 7.0 hours per night, 73% of the week, and for a mean of 18.1 months. 19 (70%) subjects were adherent regardless of age. Patients with greater improvement in AHI were more likely to be adherent. Clinical symptoms improved after positive

				airway pressure.
Marcus et al, 2006 [337]	Randomized, double-blind controlled trial	II	29 children (2-16 y.o.); diagnoses included: obesity; residual OSAS post-adenotonsillectomy; craniofacial anomaly (Treacher-Collins syndrome; Towne-Brock syndrome; Stickler syndrome); Hurler syndrome; OSAS post-renal transplantation	Patients were randomly assigned in a double-blind manner to 6 months of CPAP or NPPV. Efficacy was evaluated by polysomnography. 21 children for whom 6-month adherence data could be downloaded, the mean nightly use was 5.3 ± 2.5 hours. Positive airway pressure treatment was accompanied by reduction in AHI (from 27 ± 32 episodes/h to 3 ± 5 episodes/h) and increase in SpO_2 nadir (from 77 ± 17% to 89 ± 6%). Results did not differ among children under CPAP versus NPPV. There was a subjective improvement in daytime sleepiness.
c. *Complications of CPAP and NPPV*				
Author, year	**Type of Study**	**Class**	**Subjects**	**Methods and findings**
Korayem et al, 2013 [338]	Cross-sectional study	IV	12 patients (2 girls; mean age 9.0 years) who were treated with positive airway pressure for OSAS for at least 6 months and at least 6 hours per night. 11 control participants (6 girls; mean age 9.6 years) with OSAS who did not receive positive airway pressure. Participants had adenoidectomy (with or without tonsillectomy) but no previous orthodontic or orthognathic surgical treatment and they did not have any craniofacial syndrome.	Images generated with cone-beam volumetric imaging were used for lateral cephalometric analyses of anteroposterior projection of the midface region. No significant differences were demonstrated between patients in cephalometry variables. For children of both groups, anterior cranial base length, overall anteroposterior length of the maxillary base, and mandibular body length were shorter compared with published normative values.
Marcus et al, 2006 [337]	Randomized, double-blind controlled trial	II	29 children (2-16 y.o.); diagnoses included: obesity; residual OSAS post-adenotonsillectomy; craniofacial anomaly (Treacher-Collins syndrome; Towne-Brock syndrome; Stickler syndrome); Hurler syndrome; OSAS post-renal transplantation	Patients were randomly assigned in a double-blind manner to 6 months of CPAP or NPPV. Side effects: nasal symptoms (congestion, rhinorrhea and rarely epistaxis) occurred in 17% of patients at 48 hours and 38% of patients at 5 months. At 5 months nasal symptoms were significantly more frequent in those treated with CPAP than in those treated with NPPV ($P < 0.05$). Other side effects were rare. Skin erythema related to the mask was noted in 3% at 48 hours and in 10% at 5 months.
d. *Adherence to CPAP and NPPV*				
Author, year	**Type of Study**	**Class**	**Subjects**	**Methods and findings**

Prashad et al, 2013 [339]	Retrospective, cohort study	IV	Adolescents (n=21; age 12-18 y.o.) with OSAS treated with CPAP for at least one month and their caregivers (n=20).	Individual open-ended, semi-structured interviews were completed and objective adherence data were collected from the CPAP equipment. Seven adolescents had high use (mean use 381 ± 80 min per night), 7 had low use (30 ± 24 min per night), and 7 had no use over the previous month. Degree of structure in the home, social reactions, mode of communication among family members, and perception of benefits affected the degree of CPAP adherence.
Ramirez et al, 2013 [332]	Retrospective, cohort study	IV	62 children (mean age 10 ± 5 years) with OSAS (n=51) treated with CPAP and neuromuscular disease (n=6) or lung disease (n=5) treated with NPPV.	A sleep study was performed one month after treatment initiation. Mean adherence was 8:17 ± 2:30 h:min per night, and it did not significantly differ between children with CPAP vs. children with NPPV. 72% of the patients used their device >8 h per night. Mean number of nights with CPAP/NPPV use during the last month was 26 ± 5 nights. Treatment adherence was not associated with age, underlying disease, type of interface (nasal, facial mask, or nasal cannula), nocturnal gas exchange, and duration of positive airway pressure treatment. Mean values of nocturnal SpO_2 and transcutaneous CO_2 with CPAP or NPPV were within reference range, except for children with nasal cannula who had 8.1 ± 15.2% of night time a transcutaneous CO_2 level >50 mmHg.
DiFeo et al, 2012 [340]	Prospective, cohort study	IV	56 children (2-16 y.o.) with diagnosis of OSAS who were treated with CPAP or NPPV	Children and their parents completed a series of psychosocial questionnaires at baseline, 1 and 3 months after initiation of CPAP or NPPV. The majority of patients were obese and 23% had neurodevelopmental disabilities. The mean use was 22±8 nights during the first month for 3±3 h/night. Predictors of adherence were: maternal education (P=0.002 for nights used; P=0.033 for mean h/night). Adherence was lower in African American children compared to other races (P=0.021). In the typically developing subgroup, adherence correlated inversely with age. Adherence was not associated with severity of OSAS, pressure levels, or psychosocial parameters. During month

				3, there was a correlation between family social support and nights of using CPAP or NPPV.
Marcus et al, 2012 [341]	Randomized, double-blinded clinical trial	I	56 children and adolescents (2-16 y.o.) with OSAS due to any cause	Participants were randomized to CPAP or Bi-Flex. Repeat polysomnography was performed on pressure at 3 months. Objective adherence data were obtained at 1 and 3 months of use. There were no significant differences between CPAP and Bi-Flex regarding the number of nights that the device was turned on, or the mean number of minutes used at pressure per night (24 ± 6 vs 22 ± 9 nights, and 201 ± 135 vs 185 ± 165 min, respectively, for the first month of use). The AHI decreased significantly from 22 ± 21 episodes/h to 2 ± 3 episodes/h on CPAP (P = 0.005), and 18 ± 15 episodes/h to 2 ± 2 episodes/h on Bi-Flex (P < 0.0005), but there was no significant difference between the two study groups (P = 0.82 for CPAP vs Bi-Flex). The Epworth Sleepiness Scale decreased from 8 ± 5 to 6 ± 3 on CPAP (P = 0.14), and 10 ± 6 to 5 ± 5 on Bi-Flex (P < 0.0005; P = 0.12 for CPAP vs Bi-Flex).
Nixon et al, 2011 [342]	Retrospective, cohort study	IV	30 children (mean age 9.1 ± 5.3 years) who were treated with CPAP	Adherence to treatment was evaluated. During the first 2 to 3 months of treatment, mean CPAP use was 4.7 ± 2.7 h/night. Hours of use were not associated significantly with age, gender, baseline obstructive AHI, intellectual disability, or socioeconomic status (P > .05).
Uong et al, 2007 [336]	Retrospective, cohort study	IV	46 children (7-19 y.o.; 56% male; mean body mass index 39.8 kg/m^2) with persistent OSAS after adenotonsillectomy.	A polysomnogram was obtained before and after initiation of positive airway pressure therapy. Positive airway pressure was used on average, 7.0 hours per night, 73% of the week, and for a mean of 18.1 months. 19 (70%) subjects were adherent regardless of age. Patients with greater improvement in AHI were more likely to be adherent. Clinical symptoms improved after positive airway pressure.
Marcus et al, 2006 [337]	Randomized, double-blind controlled trial	II	29 children (2-16 y.o.); diagnoses included: obesity; residual OSAS post-adenotonsillectomy; craniofacial	Patients were randomly assigned in a double-blind manner to 6 months of CPAP or NPPV. Efficacy was evaluated

			anomaly (Treacher-Collins syndrome; Towne-Brock syndrome; Stickler syndrome); Hurler syndrome; OSAS post-renal transplantation	by polysomnography. 21 children for whom 6-month adherence data could be downloaded, the mean use per night was 5.3 ± 2.5 hours. Positive airway pressure treatment was accompanied by reduction in AHI (from 27 ± 32 episodes/h to 3 ± 5 episodes/h) and increase in SpO_2 nadir (from 77 ± 17% to 89 ± 6%). Results did not differ among children under CPAP versus NPPV. There was a subjective improvement in daytime sleepiness.
Koontz et al, 2003 [343]	Retrospective, cohort study	IV	20 children (1-17 y.o.) with OSAS, referred by physicians for noncompliance with positive airway pressure therapy.	There were e intervention groups: (1) a group receiving a 1.5-hour consultation and recommendation session; (2) a group receiving consultation and recommendations and a course of behaviour therapy; and (3) a group for whom behaviour therapy was recommended after the consultation and recommendations, but the family did not follow-up. Prior to behaviour intervention, none of the patients used the positive airway pressure device consistently. After intervention, 75% of children who received behaviour intervention (groups 1 and 2) successfully tolerated positive airway pressure therapy. Children whose families did not comply with the recommended behaviour therapy (group 3) did not increase usage of the equipment.

Question 6.8. What are the indications, efficacy and potential complications of craniofacial surgery in children with obstructive SDB?				
a + b. *Indications, efficacy and potential complications of craniofacial surgery*				
Author, year	**Type of Study**	**Class**	**Subjects**	**Methods and findings**
Tahiri et al, 2014 [344]	Systematic review	-	74 studies on isolated mandibular distraction osteogenesis including 711 children (<18 y.o.) with craniofacial abnormalities.	Mean age at the time of distraction was 18.1 months. The mean follow-up time was 28.7 months. The most frequent diagnoses were isolated Pierre Robin sequence (52.9%), syndromic Pierre Robin sequence (7%), and Treacher Collins syndrome (6.8%). Airway obstruction was treated successfully in 89.3% of cases. Success of mandibular distraction osteogenesis was defined as: decannulation of tracheostomy,

				avoidance of tracheostomy or continuous positive airway pressure, improvement of OSAS. 171 (84.2%) of the 203 tracheostomy-dependent patients were successfully decannulated. In 95.6% of 181 patients with OSAS, complete resolution or appreciable improvement of symptoms was achieved. Complications occured in 23.8% of all patients (infection with or without abscess formation, apertognathia, nerve injury, and hypertrophic scarring).
Taylor et al, 2014 [345]	Systematic review	-	16 studies including 210 patients (age 4 months to 23.2 years) with syndromic craniosynostosis and midface retrusion/hypoplasia.	The most common procedure was subcranial Le Fort III osteotomy with application of external distractor device followed by monobloc distraction osteogenesis with external device. Outcome measures used were: cephalometry in 9 studies, polysomnography in 9 studies, quantitative computed tomography in 7 studies, and frequency of decannulation in 9 studies. Polysomnography indices improved postoperatively. Upper airway volume in cephalometry or computed tomography increased and 65.7% of patients with tracheostomy were decannulated. Severe complications occurred in a few patients: meningitis (n=2), cerebrospinal fluid leak (n=13), unplanned tracheostomy (n=3), and superficial abscesses requiring incision and drainage (n=3).
Bannink et al, 2010 [346]	Retrospective, cohort study	IV	11 patients with syndromic craniosynostosis and with moderate-to-severe OSAS requiring oxygen, CPAP or tracheostomy who underwent midface advancement (mean age 14.9 years, range 4.1-23.1 years).	Outcome measures for the efficacy of midface advancement included polysomnography, upper airway endoscopy and digital volume measurement of the upper airway on CT scan. Midface advancement was effective in improving respiratory status in 6 patients and ineffective in 5. Patients who did not improve or recurred had obstruction at the level of of the rhino- or hypopharynx. These patients needed CPAP or tracheostomy despite surgery.
c. *Hyoid tongue suspension and skeletal expansion procedures in cerebral palsy or Down syndrome and craniofacial surgery in non-syndromic midface hypoplasia*				

Author, year	Type of Study	Class	Subjects	Methods and findings
Hartzell et al, 2013 [292]	Retrospective, cohort study	III	14 children with cerebral palsy.	7 patients (mean age 6 years; mean AHI 27.2 episodes/h) underwent adenotonsillectomy in combination with uvulopalatopharyngoplasty, and tongue base suspension. Another 7 patients (mean age 6.3 years; mean AHI 6.8 episodes/h) had adenotonsillectomy and uvulopalatopharyngoplasty without tongue base suspension. Preoperative and postoperative polysomnography was performed in all children. The AHI decreased by a mean of 16.5 episodes/h in the group with tongue base suspension and by a mean of 5.0 episodes/h in the group without tongue base suspension. The mean SpO_2 nadir increased in both the tongue base suspension group (from 74.0% to 84.0%) and the group without tongue base suspension (from 64.8% to 84.6%). No surgical complications were reported.
Guilleminault et al, 2004 [347]	Prospective, cohort study	IV	6 children, adolescents and young adults with OSAS and maxillary and mandibular constriction (mean age 22.2 ± 11.4 years; 2 female)	All patients underwent maxillomandibular expansion by distraction osteogenesis and the follow-up period was 18.1 ± 9.8 months. Mean maxillary expansion was 10.3 ± 3.0 mm and mean mandibular expansion was 9.5 ± 2.9 mm. Epworth Sleepiness Scale decreased from 10.2 ± 1.9 to 5 ± 2.9 and mean AHI from 13.2 ± 15.6 episodes/h to 4.5 ± 5.8 episodes/h. Mean SpO_2 nadir increased from 88.2 ± 2.9% to 91.3 ± 3.3% and mean esophageal pressure increased from -20 ± 11.3 cm H_2O to -8 ± 3.6 cm H_2O.
Cohen et al, 1998 [348]	Retrospective, cohort study	IV	20 children (age 6 days-18 years) with medically refractory OSAS and diagnosis of: craniofacial microsomia (n=6), Down syndrome (n=3), Pierre Robin syndrome (n=3), cerebral palsy (n=3), Nagers's syndrome (n=1), Treacher Collins syndrome (n = 1), cri du chat syndrome (n = 1), juvenile rheumatoid arthritis (n = 1) or temporomandibular joint ankylosis (n = 1).	14 children had severe OSAS and they were candidates for tracheostomy and 6 children had tracheostomies placed shortly after birth and could not be decannulated. All patients underwent skeletal expansion and soft-tissue reduction. Overnight, 12-channel polysomnography was performed pre- and postoperatively. The mean apnea index decreased from 7.42 episodes/h to 1.26 episodes/h, the mean respiratory disturbance index reduced from 25.24 episodes/h to 1.72 episodes/h, and the mean apnea-related SpO_2 nadir

				improved from 68% to 88%. Only 2 of 14 children who were candidates for tracheostomy finally required tracheostomy. Of the 6 patients with tracheostomies, 5 were decannulated.
Burstein et al, 1995 [349]	Retrospective, cohort study	IV	28 children and adolescents with severe upper airway obstruction, OSAS and: Down syndrome (n=5); cerebral palsy (n=12); Goldenhar syndrome (n=4); mixed diagnoses (n=7).	Tongue hyoid suspension and skeletal expansion procedures were applied. Tracheostomy was avoided in 25 of 28 patients (89%) and episodes of apnea and hypopnea decreased markedly (median decrease 90% and 87%, respectively).

6.9. What are the indications, efficacy and potential complications of tracheostomy in children with obstructive SDB?				
a+b+c. *Indications, efficacy and complications of tracheostomy*				
Author, year	**Type of Study**	**Class**	**Subjects**	**Methods and findings**
Bakor et al, 2011 [350]	Cross-sectional study	IV	Nasal breathers (n=10; mean age 13.9 y.o.); oral breathers (n=10; mean age 12.7 y.o.); and those with tracheostomy (n=10; mean age 12.8 y.o.).	Evaluation of craniofacial characteristics in children with different breathing patterns. The masseter and suprahyoid muscles were evaluated with electromyography. Facial, maxillary, and mandibular widths, nasion-sella-gnathion angle, and facial index were measured. Children with tracheostomy and nasal breathers were similar regarding greater activity of the masseter muscles than of the suprahyoid muscles during mastication, and regarding measurements of facial, maxillary, and mandibular widths. The oral group had significantly decreased measurements in each category compared to the nasal breathers. The group with tracheostomy was similar to the oral breathers during maximum dental occlusion for significantly higher activity of the suprahyoid muscles compared with the masseter muscles, with reductions in vertical values. Thus, tracheostomy is accompanied by changes in craniofacial characteristics similar to those in oral breathers.
Kremer et al, 2002 [351]	Review of the literature	-	The authors analyzed the international literature and their own experience with 25 children (< 6 y.o.) who were operated between 1980 and 1996.	Literature proved was very heterogeneous in terms of terminology, patient groups, operation techniques, indications, and complications. Long-term intubation and congenital

				anomalies of the upper respiratory tract are the most common indications for tracheostomy. Tracheostomy-related complications have not changed significantly. The most frequent causes of tracheostomy-related death are cannula obstruction and accidental decannulation. The most frequent early complications are pneumomediastinum, pneumothorax, wound complications, and bleedings. Long-term complications are development of granulation tissue and tracheal stenosis.
Cohen et al, 1998 [352]	Retrospective cohort study	IV	16 children with clinically succesful surgery for OSAS and 6 children who had tracheostomy for OSAS	Quality of life was evaluated by a 76-item questionnaire. Parents of children in the tracheostomy group ranked 95 percent of all items on the questionnaire as worse than the parents of children in the OSAS surgery group. There were statistically significant group differences ($P < 0.05$) on number of hospital, emergency room, and physician visits, and hours per day spent on the child's respiratory care. In the successful OSAS surgery group, there was significant improvement ($P < 0.05$) in choking, snoring, daytime sleepiness), assisting with the child's breathing, suctioning, perception of child's distress, worrying about the child's breathing and level of family stress. Cost was higher for OSAS surgery higher costs, it was associated with improvement in quality of life, health, and psychosocial outcomes when compared with tracheostomy.

Online Supplementary Table 7.

Step 7: Follow-up, recognition and management of persistent SDB

Question 7.1. How soon after each treatment intervention is the child with obstructive SDB usually re-evaluated and what outcomes are monitored?				
a. *Outcomes that are usually monitored after treatment interventions*				
Author, year	**Type of Study**	**Class**	**Subjects**	**Methods and findings**
Kheirandish-Gozal et al, 2014 [252]	Retrospective cohort study	IV	3,071 children (2-14 y.o.) were diagnosed with OSAS; in 836 of them OSAS was of mild severity.	Children with OSAS and obstructive AHI > 5 episodes/h were referred for adenotonsillectomy or CPAP, while those with

				obstructive AHI >1 and <5 episodes/h were recommended treatment with an intranasal corticosteroid and oral montelukast for at least 12 weeks, following which a second overnight sleep study was performed to evaluate efficacy; 752 children received montelukast and intranasal corticosteroid; 445 patients underwent follow-up polysomnography; 62% of children with mild OSAS treated with a combination of oral montelukast and nasalcorticosteroid for 12 weeks had normal sleep studies at the end of the 12 weeks period (obstructive AHI <1 episode/h). Older and obese children were significantly more likely to be non-responders (OR: 2.3; 95% CI: 1.43-4.13; P<0.001 and OR: 6.3; 95% CI: 4.23-11.18; P<0.000001, respectively).
Lee et al, 2014 [313]	Prospective, cohort study	III	144 children with SDB symptoms (mean age 7.0 ± 3.6 years; range 2-18 years; 76% boys).	Prior to adenotonsillectomy, all children underwent polysomnography and caregivers completed the OSA-18 quality of life questionnaire. A follow-up OSA-18 questionnaire was completed within 3 months after adenotonsillectomy. Disease severity was classified as: primary snoring (AHI <1 episode/h); mild OSAS (5> AHI ≥1 episodes/), and moderate-to-severe OSAS (AHI ≥5 episodes/h). Children with moderate-to-severe OSAS had greater improvement in OSA-18 postoperatively than participants with mild OSAS or primary snoring.
Volsky et al, 2014 [266]	Prospective, cohort study	III	64 children (3-16 y.o.) with mild OSAS (AHI 1-5 episodes/h); 30 patients chose adenotonsillectomy, and 34 chose observation.	At baseline, early and late follow-up visits, caregivers completed two validated quality-of-life instruments (OSA-18 and Children's Health Questionnaire). At baseline, children in the adenotonsillectomy group had significantly poorer total OSA-18 scores than those in the observation group (72.3 vs. 58.5; P=0.01). At 4 months after surgery, OSA-18 scores improved by 39.1 points compared to baseline (P = 0.0001), but there was no change in the observation group (P >0.05). At 8 months postoperatively, OSA-18 scores remained improved in the surgery group but there was no statistically significant

				difference compared to the observation group (P=0.05).
Giordani et al, 2012 [142]	Prospective cohort study	II	105 children (5-12 y.o.) with OSAS, primary snoring or controls	At one year after adenotonsillectomy there were improvements in polysomnography, sleepiness and parental reports of behavior, with mixed changes in cognitive outcomes. Children undergoing adenotonsillectomy with and without polysomnography-confirmed OSAS improved in academic achievement measures, short-term attention/working memory, executive functioning, and parental ratings of behavior. Measures of verbal abstraction ability, arithmetic calculations, visual and verbal learning, verbal delayed recall, sustained attention demonstrated declines.
Jeyakumar et al, 2012 [164]	Systematic review	-	Pediatric studies from 1980 to 2010 on the association of SDB with enuresis and the effects of adenotonsillectomy were reviewed. 14 studies were reviewed including 3,550 children (age 18 months-19 years) with SDB, of whom one-third (n = 1,113) had a diagnosis of enuresis; in 7 studies (n =1,360) frequency of enuresis was evaluated also post-adenotonsillectomy (median follow-up of 6 months; age range of 2-18 years).	Preoperative prevalence of enuresis was 31% and postoperative prevalence was 16% (P = 0.0002). Most studies did not separate primary from secondary enuresis. Some subjects probably had age-appropriate enuresis.
Marcus et al, 2012 [333]	Controlled trial	III	52 children (12 ± 4 y.o.; range 2-16 y.o.; 36 males) diagnosed with: obesity (n=36); genetic syndrome (n=9); central nervous system abnormality (n=6); craniofacial syndrome (n=3); pulmonary disease (n=3); growth hormone deficiency (n=1); Down syndrome (n=6); Prader-Willi syndrome (n=1); cerebral palsy (n=1); autism (n=1); complex chromosomal disorder (n=1).	Children underwent baseline polysomnography followed by a 2-week habituation period at home with CPAP or NPPVand a titration study. At completion of 3-month treatment, polysomnography was repeated on CPAP or NPPV and adherence data were downloaded. Neurobehavioral evaluation was performed at baseline and after 3 months of treatment. Adherence varied widely. Positive airway pressure therapy was associated with significant improvements in attention deficits (P < 0.001); sleepiness (Epworth Sleepiness Scale) (P < 0.001); behavior (P < 0.001); and caregiver- (P = 0.005) and child- (P < 0.001) reported quality of life. A significant correlation was identified between the decrease in

				Epworth Sleepiness Scale at 3 months and adherence (r = 0.411; P = 0.006). Behavioral outcomes improved in the subset of children with developmental delay.
Tagaya et al, 2012 [307]	Prospective, cohort study	IV	49 normal-weight children (1-10 y.o.) with severe or moderate OSAS (AHI ≥5 episodes/h) who underwent adenotonsillectomy.	Polysomnography was performed before adenotonsillectomy, at 2–4 months postoperatively and at 1.5 year postoperatively for children who had recurrent symptoms of SDB. Nasal endoscopy was carried out every 3 months for 1.5 years after surgery. At 1.5 years after adenotonsillectomy, 13 of 49 children had symptoms of SDB with episodes of apnea, recurrent snoring or nasal Allergic rhinitis (38.5% vs 11.1%; P = 0.03) and allergic disease (69.2% vs 30.6%; P = 0.02) were more frequent in children with recurrent symptoms compared to those who remained asymptomatic. 9 of 13 children had AHI ≥5 episodes/h and 6 children (12.2% of all children) had adenoid regrowth and three (6.1%) underwent revision adenoidectomy.
Bonuck et al, 2009 [172]	Systematic review and meta-analysis	-	20 studies analyzed (ages 5 months-15.8 years); a total of 363 children were evaluated for height change post-adenotonsillectomy and 390 subjects for weight change	Over a follow-up period ranging from 1 month to 3 years, the pooled standardized mean increase in height (z score) postoperatively was 0.34 (95% CI 0.20-0.47) and in weight 0.57 (95% CI 0.44-0.70).
Amin et al, 2008 [265]	Prospective, cohort study	II	40 children with SDB and adenotonsillar hypertrophy and 30 control children (7-13 y.o.)	Children with SDB underwent adenotonsillectomy All children were followed prospectively for 1 year. Polysomnography, body mass index, and blood pressure were obtained before adenotonsillectomy and at 6 weeks, 6 months, and 1 year postoperatively. Gain velocity in body mass index, body mass index and African American were significant predictors of SDB recurrence. In the group that experienced recurrence, systolic blood pressure at 1 year was higher compared to baseline and higher compared blood pressure in children without SDB recurrence.

Chervin et al, 2006 [260]	Prospective cohort study	II	105 children (5-12.9 y.o.): 78 scheduled for clinically indicated adenotonsillectomy, usually for SDB, and 27 for unrelated surgical care	Subjects undergoing adenotonsillectomy for suspected SDB, as compared to controls, were more hyperactive on parent rating scales, inattentive on cognitive testing, more sleepy on the Multiple Sleep Latency Test, and more likely to have attention-deficit/hyperactivity disorder as judged by a child psychiatrist. At 1 year follow-up, the 2 groups showed no significant differences in the same measures. Subjects who underwent adenotonsillectomy improved in all measures, and control subjects improved in none. Polysomnographic indices at baseline and at follow-up did not predict baseline neurobehavioral morbidity or improvement in any area other than sleepiness.
b. *Polysomnography is the recommended objective method to detect residual OSAS after a treatment intervention*				
Author, year	**Type of Study**	**Class**	**Subjects**	**Methods and findings**
Aurora et al, 2011 [8]	Practice parameters paper	-	-	-
Wise et al, 2011 [7]	Systematic review	-	-	243 evidentiary papers were analyzed and summarized.
c. *Repeat polysomnography or polygraphy after adenotonsillectomy for children with persistent symptoms or risk factors for persistent OSAS preoperatively or those treated with montelukast and nasal corticosteroid*				
Author, year	**Type of Study**	**Class**	**Subjects**	**Methods and findings**
Kheirandish-Gozal et al, 2014 [252]	Retrospective cohort study	IV	3,071 children (2-14 y.o.) were diagnosed with OSAS; in 836 of them OSAS was of mild severity.	Children with OSAS and obstructive AHI > 5 episodes/h were referred for adenotonsillectomy or CPAP, while those with obstructive AHI >1 and <5 episodes/h were recommended treatment with an intranasal corticosteroid and oral montelukast for at least 12 weeks, following which a second overnight sleep study was performed to evaluate efficacy; 752 children received montelukast and intranasal corticosteroid; 445 patients underwent follow-up polysomnography; 62% of children with mild OSAS treated with a combination of oral montelukast and nasalcorticosteroid for 12 weeks had normal sleep studies at the end of the 12 weeks period (obstructive AHI <1 episode/h). Older and obese children were significantly more likely to be non-responders (OR: 2.3; 95% CI: 1.43-4.13; P<0.001 and OR: 6.3; 95% CI: 4.23-11.18; P<0.000001, respectively).

Tagaya et al, 2012 [307]	Prospective, cohort study	IV	49 normal-weight children (1-10 y.o.) with severe or moderate OSAS (AHI ≥5 episodes/h) who underwent adenotonsillectomy.	Polysomnography was performed before adenotonsillectomy, at 2–4 months postoperatively and at 1.5 year postoperatively for children who had recurrent symptoms of SDB. Nasal endoscopy was carried out every 3 months for 1.5 years after surgery. At 1.5 years after adenotonsillectomy, 13 of 49 children had symptoms of SDB with episodes of apnea, recurrent snoring or nasal Allergic rhinitis (38.5% vs 11.1%; P = 0.03) and allergic disease (69.2% vs 30.6%; P = 0.02) were more frequent in children with recurrent symptoms compared to those who remained asymptomatic. 9 of 13 children had AHI ≥5 episodes/h and 6 children (12.2% of all children) had adenoid regrowth and three (6.1%) underwent revision adenoidectomy.
Aurora et al, 2011 [8]	Practice parameters paper	-	-	-
Wise et al, 2011 [7]	Systematic review	-	-	243 evidentiary papers were analyzed and summarized.
d. *Repeat polysomnography after rapid maxillary expansion or treatment with oral appliance*				
Author, year	**Type of Study**	**Class**	**Subjects**	**Methods and findings**
Villa et al, 2007 [326]	Prospective, cohort study	IV	16 patients (6.6 ± 2.0 y.o.) with dental malocclusion, BMI ≤ 85th percentile, and OSAS confirmed by polysomnography	Patients underwent rapid maxillary expansion and were evaluated at baseline and 1 year after the intervention. In 14 subjects who completed the study there was a significant decrease in the AHI (P=0.005) and severity of symptoms.
Cozza et al, 2004 [327]	Prospective, cohort study	IV	20 children with OSAS (10 boys; mean age 5.91 years; range 4 -8 years) and 20 healthy control children (10 boys; mean age 6 years; range 5-7 years).	Children with OSAS underwent polysomnography before and after intervention with a modified monobloc appliance. All children had cephalometric radiographs and study models. Children with OSAS demonstrated a skeletal Class II pattern with reduced mandibular length and a corresponding increase in overbite. The hyoid bone was located superiorly in the OSAS group. 6 months after the intervention in patients with OSAS, there was a significant decrease in AHI and daytime sleepiness and subjective improvement in sleep quality.

Pirelli et al, 2004 [328]	Prospective, cohort study	IV	31 children (mean age 8.7 years) with maxillary contraction, BMI < 24 kg/m^2 and OSAS diagnosed by polysomnography	Rapid maxillary expansion was performed for 10-20 days and maintenance of device and orthodontic treatment for 6-12 months. At baseline, the mean AHI was 12.2 episodes/h. At the 4-month follow-up, all children had AHI < 1 episode/h, the mean cross-sectional expansion of the maxilla was 4.32 ± 0.7 mm and the mean increase of the pyriform opening was 1.3 ± 0.3 mm.
Villa et al, 2002 [329]	Non-blinded, randomized controlled study	III	32 patients (7.1 ± 2.6 y.o.) with OSAS symptoms, malocclusion, and AHI > 1 episode/h.	19 subjects were randomly assigned to a 6-mo trial of an oral appliance and 13 subjects acted as controls. 4 treated subjects and 5 control subjects were lost to follow-up. Polysomnography after the trial showed that treated subjects had significantly lower apnea index (P < 0.001) and hypopnea index values (P < 0.001) than before the trial, whereas in untreated control subjects there was no change.
e. *Repeat polysomnography or polygraphy to assess efficacy of CPAP or NPPV treatment and to predict successful decannulation when tracheostomy is present*				
Author, year	**Type of Study**	**Class**	**Subjects**	**Methods and findings**
Amaddeo et al, 2015 [330]	Prospective, cohort study	IV	26 children (mean age 7.8 ± 6.2 years) with mean CPAP use 10.6 ± 14.4 months and the following diagnoses: Down syndrome; Treacher Collins syndrome; polymalformative syndrome; idiopathic OSAS; achondroplasia; CATCH-22 syndrome; neurofibromatosis type 1 with subglottic neurofibroma; bronchopulmonary dysplasia; Turner syndrome; Menkes syndrome; cherubism; Beckwith-Wiedemann syndrome; pycnodysostosis; Niemann–Pick disease type A; post-intubation laryngeal paralysis; Prader–Willi syndrome	Polygraphies were performed while on CPAP for 1 month and analyzed using the SomnoNIV Group definitions. 29 polygraphies were analyzed. The index of total respiratory events was low (median value 1.4 episodes/h; range 0-34 episodes/h). The mean number of different types of respiratory events per study was 2 ± 1 (range 0-4), with always a predominant event. Partial or total upper airway obstruction without a decrease in ventilatory drive was the most common event and the most frequently associated with an oxygen desaturation or an autonomic arousal.
Caldarelli et al, 2013 [331]	Prospective, cohort study	IV	39 patients (1-18 years old) who were under long-term NPPV for neuromuscular disease (n= 13), OSAS (n = 15) or lung disease (n = 11) were studied.	Polygraphy was used as a follow-up method to detect respiratory events and associated autonomic arousals or ≥3 % desaturations during nocturnal NPPV. A second polygraphy was performed following adjustment of the NPPV settings if a respiratory event occurred >50 times/h. Events recorded during monitoring were: unintentional leaks (27% of patients), patient-ventilator asynchronies (33%), decrease in ventilatory drive (10%), upper airway

				obstruction with or without reduction in ventilatory drive (11% or 12% of patients respectively). The mean duration of respiratory events was 32 ± 30 % (range 3-96 %) of total recording time. Unintentional leaks were most frequently associated with autonomic arousals, whereas patient-ventilator asynchronies were rarely associated with autonomic arousals or desaturations. 8 children had a second polygraphy and the frequency of the main respiratory event following adjustment of NPPV settings decreased (P = 0.005).
Ramirez et al, 2013 [332]	Retrospective, cohort study	IV	62 children (mean age 10 ± 5 years) with OSAS (n=51) treated with CPAP and neuromuscular disease (n=6) or lung disease (n=5) treated with NPPV.	A sleep study was performed one month after treatment initiation. Mean adherence was 8:17 ± 2:30 h:min per night, and it did not significantly differ between children with CPAP vs. children with NPPV. 72% of the patients used their device >8 h per night. Mean number of nights with CPAP/NPPV use during the last month was 26 ± 5 nights. Treatment adherence was not associated with age, underlying disease, type of interface (nasal, facial mask, or nasal cannula), nocturnal gas exchange, and duration of positive airway pressure treatment. Mean values of nocturnal SpO_2 and transcutaneous CO_2 with CPAP or NPPV were within reference range, except for children with nasal cannula who had 8.1 ± 15.2% of night time a transcutaneous CO_2 level >50 mmHg.
Marcus et al, 2012 [333]	Controlled trial	III	52 children (12 ± 4 y.o.; range 2-16 y.o.; 36 males) diagnosed with: obesity (n=36); genetic syndrome (n=9); central nervous system abnormality (n=6); craniofacial syndrome (n=3); pulmonary disease (n=3); growth hormone deficiency (n=1); Down syndrome (n=6); Prader-Willi syndrome (n=1); cerebral palsy (n=1); autism (n=1); complex chromosomal disorder (n=1).	Children underwent baseline polysomnography followed by a 2-week habituation period at home with CPAP or NPPVand a titration study. At completion of 3-month treatment, polysomnography was repeated on CPAP or NPPV and adherence data were downloaded. Neurobehavioral evaluation was performed at baseline and after 3 months of treatment. Adherence varied widely. Positive airway pressure therapy was associated with significant improvements in attention deficits (P < 0.001); sleepiness

				(Epworth Sleepiness Scale) ($P < 0.001$); behavior ($P < 0.001$); and caregiver- ($P = 0.005$) and child- ($P < 0.001$) reported quality of life. A significant correlation was identified between the decrease in Epworth Sleepiness Scale at 3 months and adherence ($r = 0.411$; $P = 0.006$). Behavioral outcomes improved in the subset of children with developmental delay.
Aurora et al, 2011 [8]	Practice parameters paper	-	-	-
Wise et al, 2011 [7]	Systematic review	-	-	243 evidentiary papers were analyzed and summarized.
Tan et al, 2007 [353]	Retrospective, cohort study	IV	61 sleep studies were performed for evaluation of mechanical respiratory support in 45 children (27 boys; median age 8.3 years; range 0.4-18.6 years).	27% of the children (*n* = 12) had craniofacial abnormalities, 20% (*n* = 9) neuromuscular disorder (Duchenne muscular dystrophy), 20% (*n* = 9) a central nervous disorder (spina bifida, central congenital hypoventilation), 18% (*n* = 8) were obese and 15% (*n* = 7) had another diagnosis (diaphragm dysfunction). Twenty-nine (64%) children were on CPAP, 14 (31%) on NPPV and two (4%) on mechanical ventilation via tracheostomy. In 66% of cases, adjustments were necessary in parameters of positive airway pressure.
Mukherje et al, 1999 [354]	Retrospective, cohort study	IV	31 children (<12 y.o.) who had a tracheostomy for ≥6 months	Decannulation was appropriate based on clinical, radiological and endoscopic findings in all 31 patients. 21 of 22 patients with favorable polysomnography findings were decannulated successfully. Attempts to decannulate 9 patients with non-favourable polysomnography findings were unsuccessful.
Tunkel et al, 1996 [355]	Retrospective, cohort study	IV	52 children (median age 37 months; range: 16 months-11 years), with tracheostomy due to: craniofacial disorders (n=7); subglottic stenosis (n=4); OSAS and/or neuromotor disease; n=7); and ventilator dependence (n=6). Mean duration of cannulation was 28 months (range: 3 months to 10 years).	All patients underwent polysomnography to evaluate readiness for decannulation. 16 children had polysomnography rsults favorable for decannulation. The obstructive index was less than 1.7 events/h and 14 (88%) of them had obstructive index <1.0 event/h. All 16 patients had less than 2.7 central events/h and 13 (81%) had less than 1.0 central event/h. Mean SpO_2 during sleep was >95%. Range of mean end-tidal CO_2 during sleep was 38-46

				mmHg and range of maximum end-tidal CO_2 was 42-51 mm Hg. 13 of these 16 patients were decannulated successfully. 8 children had polysomnography results that were unfavorable for decannulation. 6 of 8 (75%) children developed obstructive symptoms within minutes of occlusion of the tracheostomy tube during sleep; 1 child had paradoxical sustained breathing pattern when the tracheostomy tube was occluded and 1 child developed hypercapnia.
f. *Nasopharyngoscopy, drug-induced sleep endoscopy and MRI*				
Nasopharyngoscopy				
Author, year	**Type of Study**	**Class**	**Subjects**	**Methods and findings**
Tagaya et al, 2012 [307]	Prospective, cohort study	IV	49 normal-weight children (1-10 y.o.) with severe or moderate OSAS (AHI ≥5 episodes/h) who underwent adenotonsillectomy.	Polysomnography was performed before adenotonsillectomy, at 2–4 months postoperatively and at 1.5 year postoperatively for children who had recurrent symptoms of SDB. Nasal endoscopy was carried out every 3 months for 1.5 years after surgery. At 1.5 years after adenotonsillectomy, 13 of 49 children had symptoms of SDB with episodes of apnea, recurrent snoring or nasal Allergic rhinitis (38.5% vs 11.1%; P = 0.03) and allergic disease (69.2% vs 30.6%; P = 0.02) were more frequent in children with recurrent symptoms compared to those who remained asymptomatic. 9 of 13 children had AHI ≥5 episodes/h and 6 children (12.2% of all children) had adenoid regrowth and three (6.1%) underwent revision adenoidectomy.
Thevasagayam et al, 2010 [356]	Retrospective, cohort study	IV	358 children with SDB who underwent sleep nasopharyngoscopy.	14 (3.9%) children were diagnosed with laryngomalacia. 3 of 14 children were syndromic and 1 had cerebral palsy. 3 of 14 children were obese, and 3 had had gastroesophageal reflux. 7 of 14 children (50%) had snoring and/or swallowing dysfunction and/or stridor in infancy. 12 patients underwent adenotonsillectomy and symptoms resolved in 8 cases whereas in 6 patients a supraglottoplasty was performed with

				3 failures to supraglottoplasty.
Drug-induced sleep endoscopy				
Author, year	**Type of Study**	**Class**	**Subjects**	**Methods and findings**
Fishman et al, 2013 [357]	Retrospective case series	IV	28 children with persistent OSAS	Awake and drug-induced sleep endoscopy were performed. Two pediatric otolaryngologists and two pediatric pulmonologists scored each recording using an upper airway endoscopy scoring survey. Sleep endoscopy had a better interobserver correlation and identified more cases of obstruction at the nasopharynx, lateral pharyngeal walls, tongue base and supraglottis compared to awake endoscopy.
Ulualp et al, 2013 [358]	Retrospective, cohort study	IV	82 children (mean age 6 ± 3.7 years; 1.5-17 years) and the following comorbid conditions: asthma (n=10), seizure disorder (n=3), Down syndrome (n=2), congenital heart disease (n=1), autism (n=1), sickle cell disease (n=1), chronic lung disease (n=1), and neurofibromatosis (n=1). 4 patients had mild OSAS; 17 patients had moderate OSAS; 61 patients had severe OSAS.	All children had drug-induced sleep endoscopy. Obstruction was identified at the level of: velum (n=67), oropharynx/lateral walls (n=72), tongue (n=10), and epiglottis (n=10). Obstruction most commonly occurred at the level of the oropharynx/lateral walls. The majority of children had obstruction at multiple sites (e.g. velum and oropharynx/lateral walls). Frequency of complete obstruction at the velum and oropharynx/lateral walls was higher in children with moderate-severe OSAS than in those with mild OSAS.
Durr et al., 2012 [359]	Retrospective case series	IV	13 children (3-15 y.o.) with persistent OSAS after adenotonsillectomy	All patients had drug-induced sleep endoscopy. Multilevel upper-airway obstruction (tongue base obstruction, adenoid regrowth, and/or inferior turbinate hypertrophy) was identified in the majority of patients with persistent OSAS after adenotonsillectomy.
Fung et al, 2012 [61]	Case-control study	III	Over a period of 4.5 years, 23 children with Down syndrome (7 girls; mean age 7.09 ± 4.37 years) and persistent snoring or SDB; 23 matched controls for age, gender, and BMI-percentile (mean age 7.6 ± 4.14 years).	Children underwent sleep nasopharyngoscopy under intravenous sedation. Children with Down syndrome had more frequently pharyngeal or lingual collapse than the controls. The two groups did not differ regarding frequency of tonsillar hypertrophy.
Truong et al., 2012 [360]	Retrospective case series	IV	80 children (mean age 6 ± 3.75 years) with OSAS confirmed by polysomnography who underwent sleep endoscopy and surgery based on the endoscopy findings.	28% of chidren had co-morbidities. AHI decreased after surgery. Sleep endoscopy is a useful and reliable tool for evaluation of subjects with OSAS, especially children with persistent

				OSAS after adenotonsillectomy, children with OSAS without tonsil or adenoid hypertrophy, or children with significant co-morbidities.
Revell et al., 2011 [361]	Retrospective case series	IV	77 children with OSAS diagnosed by polysomnography and airway endoscopy for the evaluation of laryngomalacia. Children with neurologic disease or craniofacial malformations were excluded. 7 children < 3 y.o. had laryngomalacia and OSAS (Group A); 19 children 3-18 y.o. had laryngomalacia and OSAS (Group B), and 51 children 3-18 y.o. had OSAS but not laryngomalacia (Group C).	Group A had similar presentation, diagnosis and treatment to previous reports of congenital laryngomalacia in the literature. Groups B and C had similar pre-operative findings, a high frequency of adenotonsillar hypertrophy, and the only difference was the intra-operative finding of laryngomalacia in Group B. Treatments were individualized to include supraglottoplasty, adenoidectomy, tonsillectomy, adenotonsillectomy, or a combination of the above. Of the 52 patients who returned for follow-up, 44 had improved. Drug-induced sleep endoscopy can identify the presence of laryngomalacia as a contributor to OSAS in children.
MRI				
Author, year	**Type of Study**	**Class**	**Subjects**	**Methods and findings**
Nandalike et al, 2013 [305]	Prospective, cohort study	IV	27 obese children with OSAS (age 13.0 ± 2.3 years; body mass index Z-score 2.5 ± 0.3)	Children underwent polysomnography and MRI of the head during wakefulness before and after adenotonsillectomy (6.1 ± 3.6 months postoperatively). Obstructive AHI decreased from 23.7 ± 21.4 episodes/h to 5.6 ± 8.7 episodes/h (P < 0.001). OSAS resolved in 44% children (12 of 27 patients), but only in 22% (4 of 18) of children with severe OSAS (AHI > 10 episodes/h). The volume of the nasopharynx and oropharynx increased. However, volumes of the adenoid, lingual tonsil, or retropharyngeal nodes did not change, whereas volumes of the tongue and soft palate increased. Obese children with OSAS have residual adenoid tissue and an increase in the volume of the tongue and soft palate following adenotonillectomy.
Donnelly et al, 2004 [362]	Cross-sectional study	IV	27 children with Down syndrome and persistent OSAS after adenoidectomy and tonsillectomy (mean age 9.9 years)	All children underwent cine MRI studies of the upper airway under sedation. Abnormalities found included: glossoptosis in 17 patients (63%), hypopharyngeal collapse in 6 (22%), recurrent and enlarged adenoid tonsils in

				17 (63%), enlarged lingual tonsils in 8 (30%), and macroglossia in 20 (74%). Abnormalities in patients with macroglossia included absence of the normal median sulcus (11 cases or 55%) and fatty infiltration of the tongue musculature (12 cases or 60%).
Shott et al, 2004 [62]	Cross-sectional study	IV	15 children with Down syndrome and abnormal polysomnography after adenotonsillectomy	Patients underwent cine MRI and different areas of upper airway obstruction were demonstrated including recurrent adenoidal tissue, glossoptosis, soft palate collapse, hypopharyngeal collapse, and enlarged lingual tonsil.

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