AHA SCIENTIFIC STATEMENT

Sleep-Disordered Breathing and Cardiovascular Disease in Children and Adolescents

A Scientific Statement From the American Heart Association

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ABSTRACT: Obstructive sleep apnea (OSA) is a known risk factor for cardiovascular disease in adults. It is associated with incident systemic hypertension, arrhythmia, stroke, coronary artery disease, and heart failure. OSA is common in children and adolescents, but there has been less focus on OSA as a primary risk factor for cardiovascular disease in children and adolescents. This scientific statement summarizes what is known regarding the impact of sleep-disordered breathing and, in particular, OSA on the cardiovascular health of children and adolescents. This statement highlights what is known regarding the impact of OSA on the risk for hypertension, arrhythmia, abnormal ventricular morphology, impaired ventricular contractility, and elevated right heart pressure among children and adolescents. This scientific statement also summarizes current best practices for the diagnosis and evaluation of cardiovascular disease–related complications of OSA in children and adolescents with sleep apnea and highlights potential future research in the area of sleep-disordered breathing and cardiovascular health during childhood and adolescence.

Key Words: AHA Scientific Statements ■ arrhythmia ■ cardiovascular disease ■ left ventricular hypertrophy ■ obstructive sleep apnea ■ pediatric ■ sleep-disordered breathing ■ systemic hypertension

Obstructive sleep apnea (OSA) is associated with cardiovascular disease (CVD) in adults.[1-3] Cross-sectional and longitudinal studies have demonstrated a relationship between OSA and systemic hypertension, arrhythmia, coronary artery disease, stroke, and all-cause CVD-related morbidity and mortality.[1,4–10] Fewer studies have demonstrated a relationship between OSA and cardiovascular health among children and adolescents.[11] OSA results in disrupted sleep. Shorter sleep duration[12] has been linked to a greater odds of hypertension in some but not all studies,[11] and OSA as diagnosed via polysomnography testing has been associated with a greater prevalence of left ventricular hypertrophy (LVH) in children and adolescents.[13] Associations between OSA and CVD risk factors, such as hypertension, arrhythmia, ventricular remodeling, and right heart hypertension in children and adolescents deserve further attention and are the focus of this scientific statement. Associations between OSA and cognitive and behavioral disorders, such as attention deficit hyperactivity disorder, are beyond the scope of this statement and have been well described in other published reviews.[14-17] This statement briefly discusses approved treatments for OSA, as a detailed review of therapeutic options can be found elsewhere.[16,18]

CLINICAL PRESENTATION OF SLEEP-DISORDERED BREATHING AND OSA: SYMPTOMS AND SIGNS IN CHILDREN AND ADOLESCENTS

Sleep-disordered breathing (SDB) is a spectrum of conditions that includes primary snoring, upper airway resistance syndrome, obstructive hypoventilation, and OSA (Figure 1).[19] The clinical presentation of OSA in children and adolescents can vary by age and includes symptoms and signs of upper airway obstruction. Habitual snoring (≥3 nights/wk), labored breathing during sleep, gasps/snorting noises, sleeping in a seated position or with the neck hyperextended, headaches on awakening, and daytime sleepiness may all be associated with the presence of OSA in children and adolescents.[16] In certain populations, these manifestations are not present, so maintenance of a high degree of clinical suspicion is recommended to detect OSA.[16,20] Reliance on physical examination findings, such as tonsillar size, may not correlate well with the degree of airway obstruction (Figure 2).[16,21] Other grading systems for assessing pharyngeal anatomy, such as the Mallampati score and the Friedman palate position, have also not been shown to correlate well with severity of airway obstruction.[16]

DIAGNOSTIC EVALUATION OF SDB AND OSA SYNDROME

Diagnosis

According to the American Academy of Otolaryngology–Head and Neck Surgery (AAO–HNS), polysomnography is the gold standard for diagnosing sleep-disordered breathing in children, including OSA.[23] Polysomnography is recommended before tonsillectomy in children with SDB who have conditions that increase their risk for complications of surgery, such as obesity, Down syndrome,[23,24] craniofacial abnormalities (eg, Pierre-Robin sequence and cleft palate),[23,25,26] neuromuscular disorders (eg, muscular dystrophy), sickle cell disease (SCD), or mucopolysaccharidoses.[23] Children with Down syndrome have adenotonsillar hypertrophy, midface and mandibular

hypoplasia, relative macroglossia, glossoptosis, generalized muscular hypotonia, and obesity, increasing their risk for airway obstruction. Younger children with syndromes resulting in craniofacial malformations are at a particularly high risk for OSA.[27] Polysomnographic criteria for diagnosing OSA include (1) ≥1 obstructive events (obstructive or mixed apnea or obstructive hypopnea) per hour of sleep or (2) obstructive hypoventilation (eg, end-tidal CO_2 >50 mm Hg for >25% of the tested sleep time) coupled with snoring, paradoxical chest and abdominal wall movement, or flattening of the nasal airway waveform.[28] SDB includes primary snoring, upper airway resistance syndrome, obstructive hypoventilation, and OSA syndrome,[28] but, excluding primary snoring, OSA is the most common.[2]

Childhood OSA, as in adults, is predominantly a rapid eye movement (REM)–related disease, with more frequent and longer apneas and greater desaturation during REM versus non-REM sleep.[29] Although REM sleep typically occurs during the latter portion of the sleep cycle and apnea is more common during REM sleep, apnea severity worsens over the course of the night, independent of REM sleep.[29] An important distinction between childhood OSA and adult OSA is that children with OSA syndrome demonstrate lower apnea-hypopnea index (AHI) compared with adult-OSA syndrome, despite similar severity in oxygen desaturation and clinical presentation.[30]

In adults, OSA has significant effects on sleep architecture.[31] Adults with severe OSA have a lower percentage of slow-wave sleep. They also have higher percentages of the lighter stages of sleep (N1 and N2). Overall, the arousal index and respiratory-related arousal index increase with higher OSA severity in adults.[31] This high arousal index is reflected in increased sleep fragmentation; increased sleep fragmentation is correlated with increases in sleepiness measures and decreases in measures of cognitive function. In contrast, children with OSA have been shown to have less cortical arousal after respiratory disturbances.[29,32,33] This higher arousal threshold in response to OSA in children and adolescents may result in less sleep fragmentation.[32]

The diagnosis of OSA is based on a combination of clinical and polysomnographic criteria. The evaluation of a child with suspected OSA begins with a thorough history and physical examination. OSA can cause both nighttime and daytime symptoms, and children and adolescents should be assessed for both. Physical examination includes an assessment of growth and detailed examination of the upper airway, including the nose and oropharynx for signs of adenotonsillar hypertrophy.[16]

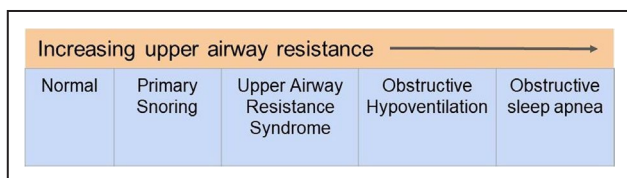History and physical examination, however, have low sensitivity and specificity for diagnosing OSA

Increasing upper airway resistance ➝				
Normal	Primary Snoring	Upper Airway Resistance Syndrome	Obstructive Hypoventilation	Obstructive sleep apnea

Figure 1. Sleep-disordered breathing.
Obstructive sleep apnea syndrome.[19] Adapted from Carroll.[19] Copyright 2003, with permission from Elsevier.
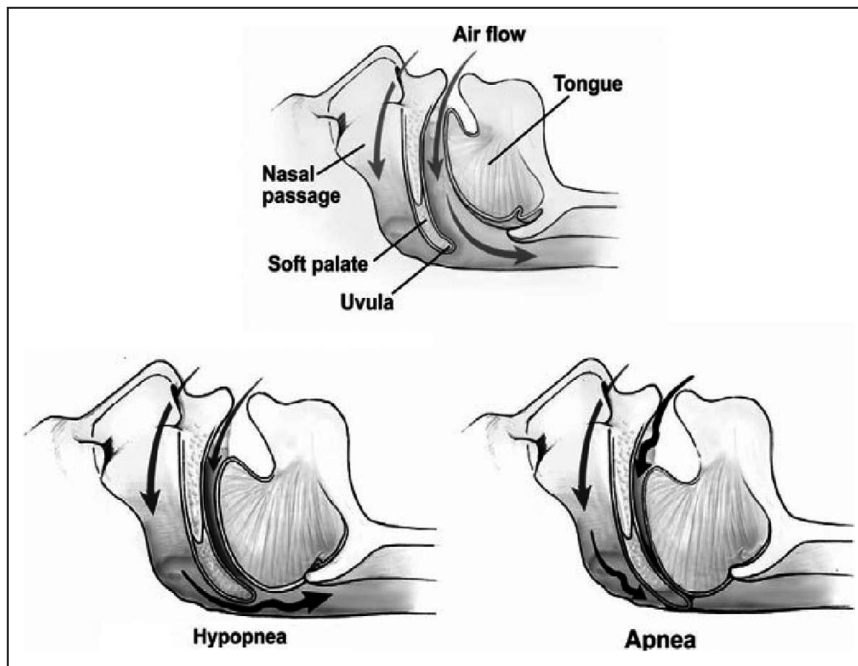
Figure 2. **Partial and complete airway obstruction resulting in hypopnea and apnea, respectively.**
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and cannot be used to reliably distinguish a primary snorer from one with OSA[18] or for making a diagnosis of OSA[23,34] or the severity of OSA.[35] Clinical assessment of tonsillar size (Brodsky score) is a weak predictor of the presence or severity of OSA.[16] Overnight polysomnographic testing is considered the gold standard for diagnosing OSA by the American Thoracic Society, the American Academy of Pediatrics (AAP),[18] and the American Academy of Sleep Medicine,[16,18] while the AAO–HNS recommends polysomnography only for suspected OSA in children with obesity, Down syndrome, craniofacial abnormalities, neuromuscular disorders, SCD, or mucopolysaccharidoses.[23] In children without these conditions and in whom the need for surgery is uncertain, or where there is discordance between the physical examination and the reported severity, the AAO–HNS also advocates for polysomnography before tonsillectomy. Studies have shown that a single-night polysomnography is adequate for diagnosis, as there is very little night-to-night variability.[36]

Metrics provided by polysomnography for the diagnosis of OSA include the AHI. The AHI is the number of apneas, hypopneas, and mixed apneas per hour of sleep (Table).[21,22] The respiratory disturbance index includes respiratory effort–related arousals in addition to the AHI. In pediatric laboratories that do not score respiratory effort–related arousals, the AHI is similar to the respiratory disturbance index. An AHI of >1 event/h is considered statistically abnormal in children.[28,34,36] Pediatric OSA can be categorized as mild (AHI of 1–4 events/h), moderate (5–9 events/h), or severe (≥10 events/h).[36] Other variables that are considered

when attempting to classify OSA severity include gas exchange abnormalities and the degree of sleep fragmentation.

Severity assessment based on the polysomnogram enables the clinician to stratify surgical risk, predict morbidity, plan for postoperative management, and determine the likelihood of persistent disease. However, in areas where sleep laboratories with pediatric expertise are not available, alternative tests may need to be considered.[18] These alternative tests have weaker positive and negative predictive values when compared with polysomnography. They include daytime nap polysomnography, nocturnal oximetry, and nocturnal video recording.[18] However, polysomnography is currently the only test that can reliably distinguish primary snoring from OSA.[18] Home sleep apnea tests are now part of the clinical practice guideline for diagnosing OSA in adults,[38] but the use of home sleep apnea tests is not recommended for diagnosing OSA in children.[39] Because most home sleep apnea tests do not include end-tidal CO_2 and electroencephalographic monitoring, their use may lead to an underestimation of the presence and severity of OSA because of an inability to assess hypoventilation and arousals.

Additional measures used for diagnosing OSA in children and adolescents include questionnaires validated to assess signs and symptoms associated with OSA. These questionnaires are useful as screening but not as diagnostic tools and may be best suited for research purposes. An example is the Sleep-Related Breathing Disorder scale from the well-validated Pediatric Sleep Questionnaire.[40] The Sleep-Related Breathing Disorder

Table 1. Definition of Terms

Term	Definition
Apnea	Repetitive interruption of ventilation during sleep caused by collapse of the pharyngeal airway. Cessation of airflow >2 breaths in duration for children and adolescents and >10 s for adults
AHI	Frequency of apneas and hypopneas per hour of sleep; measure of OSA severity
Arousal	Abrupt change in EEG frequency lasting at least 3 s with at least 10 s of stable sleep preceding the change, with concurrent increase in chin EMG for at least 1 s during REM sleep
Hypopnea	Reduction in airflow signal amplitude of at least 30%, in the presence of chest/abdominal wall motion, associated with oxygen desaturation of hemoglobin ≥3% or with an arousal
Hypoventilation	P_{CO_2} >50 ppm
NREM sleep	NREM or quiet sleep
Obstructive hypoventilation	Gas exchange abnormalities without discrete obstructive apneas
OSA	Prolonged upper airway obstruction and intermittent complete obstructions leading to disruptions in normal ventilation during sleep
Polysomnography	Multichannel electrophysiologic recording that captures respiratory activity, EEG, EMG, and EOG recordings
Primary snoring	Snoring is a respiratory sound generated in the upper airway during sleep. Primary snoring is snoring that is not associated with apneas or gas exchange abnormalities.
REM sleep	REM or active sleep; associated with skeletal muscle atonia, rapid movements of the eyes, and dreaming
Sleep efficiency	Defined as the proportion of time spent asleep while in bed (or during recording time in a sleep study)
SDB	Defined by the degree of upper airway resistance, presence of sleep arousals, abnormalities in gas exchange, and apnea; includes primary snoring, upper airway resistance syndrome, obstructive hypoventilation, and OSA syndrome
Upper airway resistance syndrome	Increased upper airway resistance sufficient to degrade sleep quality; causes increased work of breathing leading to frequent arousals; no associated gas exchange abnormalities

AHI indicates apnea-hypopnea index; EEG, electroencephalographic; EMG, electromyogram/electromyographic; EOG, electrooculographic; NREM, nonrapid eye movement; OSA, obstructive sleep apnea; REM, rapid eye movement; and SDB, sleep-disordered breathing.

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scale has been shown to have a sensitivity of 81% and a specificity of 87% for polysomnography-defined OSA.[41] It is effective as a screen to identify children at high versus low risk for OSA.[42-46] Another validated questionnaire used in the evaluation of sleepiness, but not OSA, in children and adolescents is the Epworth Sleepiness Scale for Children and Adolescents (ESS-CHAD). The ESS-CHAD is a reliable and an internally valid measure of daytime sleepiness in adolescents 12 to 18 years of age.[47]

Children undergoing evaluation for OSA should also be screened for conditions that may reflect associated morbidity, including those affecting the cardiovascular system such as hypertension and metabolic syndrome (MetS).[48] An assessment of the central nervous system and screening for comorbid behavioral disorders is also recommended.[16]

Because snoring or other nonubiquitous OSA symptoms are often used to identify subjects eligible for pediatric polysomnography, underestimation of OSA prevalence may occur, especially if there is a failure to recognize symptoms of OSA by parents or if clinical signs are absent. Finally, complete laboratory-based polysomnography remains a resource-intensive procedure, and therefore the sample sizes of children studied with polysomnography are relatively small.[49] In conclusion, diagnosing OSA in children and adolescents requires a high index of suspicion and, although the diagnosis may be made on the basis of clinical findings, polysomnography is considered to be the gold standard by the American Thoracic Society, AAP, and American Academy of Sleep Medicine, and AAO–HNS. However, according to the AAO–HNS, the premise for the need for polysomnography before tonsillectomy and adenoidectomy in children 2 to 18 years of age is if the indication for surgery is SDB, and the child has conditions that increase risk for complications from surgery, such as obesity, Down syndrome, craniofacial abnormalities, neuromuscular disorders, SCD, or mucopolysaccharidoses.

Epidemiology

OSA is common among children and adolescents. It disrupts the normal restorative properties of sleep, thereby negatively impacting the emotional, metabolic, immunologic, and cardiovascular health of children and adolescents.[50] Approximately 1% to nearly 6% of all children and adolescents have OSA.[16,18]

The prevalence of OSA peaks between 2 and 8 years of age, corresponding to a peak prevalence of adenotonsillar hypertrophy.[20] Variations in estimated prevalence of OSA are likely attributable to differences in definition,[18] as well as differences in reliance on clinical versus polysomnographic criteria for diagnosing OSA. The criteria within studies used to define OSA vary and thus impact reported prevalence, as does the age of the children studied and their comorbid conditions.[16,18,49]

Risk Factors

There have been several pathophysiologic mechanisms proposed to explain the presence of OSA in

affected children and adolescents, including the size of the pediatric airway, which is dependent on craniofacial and soft tissue structures; increases in upper airway resistance, including narrowing/retropositioning of the maxilla/mandible; adenotonsillar hypertrophy; and the stability of the upper airway based on neuromuscular activation, arousal threshold, and ventilatory control.[51] A detailed description of the these various proposed pathophysiologic mechanisms is beyond the scope of this statement and can be found elsewhere.[51] Knowledge of the primary sites of anatomic obstruction in OSA facilitates a greater understanding of the potential risk factors for OSA in children and adolescents.

The primary sites of anatomic obstruction among persons with OSA are at the levels of the nasal, palatal, and hypopharyngeal airway. Persons with increased risk for collapse of the upper airway because of anatomic and neuromuscular disease are at particularly high risk. Thus, risk factors contributing to the presence of OSA in children and adolescents have been determined to be obesity, particularly among children <6 years of age, where younger age (<6 years) and body mass index (BMI) Z-score >1.036 is associated with a 6.5 times greater odds of OSA compared with older age and BMI Z-score >1.036[52]; upper and lower airway disease[53]; hypotonia; parental history of adenotonsillar hyperplasia[54]; craniofacial malformations[34]; neuromuscular disorders; and allergic rhinitis.[16,55] Because of the relationship between craniofacial malformations and OSA, the prevalence of OSA among children and adolescents with clinical syndromes such as Apert, Crouzon, and Pfeiffer syndrome is very high. It is estimated that OSA is prevalent in roughly 60% of children with Apert and Crouzon syndromes and in 46% of children with Pfeiffer syndrome.[56] Marked mandibular hypoplasia is a risk factor for airway obstruction as occurs in cases of Pierre Robin sequence (eg, triad of micrognathia, glossoptosis, and upper airway obstruction),[26] Treacher Collins,[57] Nager,[58] and Stickler syndromes.[58] The reported prevalence of OSA in children with Pierre Robin sequence is 46% to 85%, but advancing age in this group may result in improvements in the degree of OSA during the first year of life as the mandible grows, thus allowing for more conservative management.[26] OSA also occurs among 8.5% of youth with unrepaired and repaired cleft palate.[59] Approximately 14.7% of children with isolated cleft lip/palate have OSA. Children with cleft lip/palate have abnormal craniofacial structure and anatomic changes to the nose, nasopharynx, oropharynx, and palate that contribute to airway obstruction.[60] Neuromuscular disorders, including cerebral palsy, Duchenne muscular dystrophy,[61] and myotonic muscular dystrophy, are associated with poor muscle tone and consequent airway collapse contributing to the risk for OSA. All

people with DMD will eventually develop SDB attributable to progressive decline in neuromuscular function.[62] Complex abnormalities such as achondroplasia and epilepsy have also been associated with OSA. People with achondroplasia have a reported prevalence of OSA of 20% to 32% that is thought to be at least partially related to the presence of midface hypoplasia.[63] It is unclear if seizures increase the risk for OSA or if OSA increases the risk for refractory seizures, but a relationship has been demonstrated.[64] Physical findings of overweight status, tonsillar hypertrophy, micrognathia, retrognathia, and high arched palate contribute to further airway narrowing and are associated with an increased risk for OSA.[18] Premature birth (<36 weeks' gestation) has also been identified as a risk factor for OSA. Children who were delivered preterm may be at increased risk for SDB, partly because of exposures within the perinatal environment influencing the development of respiratory control or upper airway size. However, the risk of apnea appears to decrease with increasing postgestational age.[65] Some studies, but not all, have identified male sex as a risk factor for OSA.[65]

There are limited data to support that children with congenital heart disease (CHD) may be at greater risk for SDB and OSA. A small (n=14) prospective case-control study estimated that SDB was prevalent in roughly 11 of the 14 infants with CHD. Investigators reported a higher AHI among infants with acyanotic and cyanotic CHD (2.4 and 2.5, respectively) versus among infants without CHD (AHI, 0.7).[66] A small, uncontrolled, observation study of 15 infants with single-ventricle physiology found that 14 of the 15 had an AHI >1/h.[67] A larger, retrospective study of 461 778 children with CHD included in the administrative Kids' Inpatient Database between 1997 and 2012 found that 4839 had SDB, with 14% meeting criteria for OSA. However, only central apnea (4% of the infants) and not OSA was associated with increased mortality, while OSA and central apnea were associated with longer hospital stay and increased total charges when compared with infants without SDB.[68]

Social constructs (eg, race) and economic factors may be associated with both the prevalence of OSA and access to care.[69] Black American race has been reported as a risk factor for OSA (odds ratio [OR], 5.0; 95% CI, 1.8–14.0).[53,65] According to data from the Cleveland Children's Sleep and Health Study that categorized the sleep, breathing, and general health of 907 children 8 to 11 years of age using questionnaires and in-home overnight sleep study data, Black American race, even when adjusting for preterm birth (<36 weeks) and BMI, was shown to be a significant risk factor for OSA (OR, 4.9; 95% CI, 1.7–17.8),[65] but mechanisms mediating this relationship require further determination,[70] as degree of adenotonsillar

hypertrophy and socioeconomic factors may be potential confounders.[71] In fact, a cross-sectional study by Wang et al[72] found that the relationship between Black American race and OSA prevalence and severity in children is no longer significant after controlling for neighborhood socioeconomic variables such as poverty rate and percentage of single-female–headed households. These results highlight that neighborhood socioeconomic factors likely explain perceived racial differences in OSA prevalence and severity among children. Historically, studies have been insufficiently powered to determine whether other races are at greater risk for OSA.[65] The impact of potential confounders such as daily stressors, racial/social inequality and racism, housing inequities, environmental pollutants, and sleep duration on reported prevalence among this population have yet to be determined and deserves further attention.[70] It is difficult to make wide assumptions regarding the relationship between race or ethnicity and sleep quality; further data are needed to verify and explain this reported relationship. Furthermore, differences in treatment strategy deserve further attention as it has been shown that Black American children are less likely to undergo adenotonsillectomy independent of socioeconomic status.[69]

Children and adolescents with allergic rhinitis are at risk for airway obstruction, particularly youth with allergic rhinitis and adenotonsillar hypertrophy.[73] Allergic rhinitis is common, affecting roughly 10% to 40% of all persons.[73] Adenotonsillar hypertrophy is present in largely 90% of children and adolescents with allergic rhinitis, contributing to the relationship between allergic rhinitis and OSA.[73] Inflammatory factors and chemical mediators released in children and adolescents with allergic rhinitis may play an important role, contributing to the presence of OSA. A recent meta-analysis of data from 44 studies from across the world assessed the relationship between allergic rhinitis and OSA. The mean age of children studied was 7.7±3 years. Among children, the prevalence of OSA was 45.2%.[73] Perioperative administration of albuterol in a randomized clinical controlled trial among children and adolescents at the time of adenotonsillectomy has been shown to reduce rates of airway obstruction, decrease airway inflammation, and lead to more favorable outcome at the time of tonsillectomy.[74]

Finally, SCD is a reported risk factor for OSA.[23] In fact, it has been reported that SCD is an independent risk factor for OSA with a reported prevalence that is higher than that among Black American children without SCD.[75]

Risk factors for OSA may vary with age.[76] Forty-nine percent of 5- to 9-year-old candidates for tonsillectomy who were randomly assigned to no intervention had resolution of polysomnographic evidence of OSA beginning at 7 months after diagnosis.[77] A single longitudinal study found that the only risk factor for OSA that persisted from middle childhood (8–11 years of age) into adolescence (16–19 years of age) was obesity.[76] Habitual snoring, living in an underresourced neighborhood, premature birth, obesity, and Black American race were risk factors for OSA between 8 and 11 years of age, but only obesity was associated with a greater incidence of OSA in middle childhood and in adolescence. Other risk factors for OSA by cross-sectional analysis in youth (16–19 years of age), when adjusted for obesity status, included male sex (adjusted OR, 10.63; 95% CI, 2.45–46.16), history of tonsillectomy (adjusted OR, 3.37; 95% CI, 1.18–9.62) or adenoidectomy (adjusted OR, 4.81; 95% CI, 1.96–11.85) and obesity in middle childhood.[76]

Data suggest that although it is important to be aware of risk factors for OSA in childhood, obesity is the main risk factor, and families and health care professionals should be counseled regarding this relationship.

As in adults, the presence of increased inflammation, among children with obesity, may explain the relationship between obesity and OSA.[78] An initial cross-sectional analysis of data from the Penn State Child Cohort study revealed that increases in inflammatory markers (eg, elevated C-reactive protein) mediate an association between visceral adiposity and OSA in adolescents.[79] A follow-up longitudinal study evaluating the relationship between serum C-reactive protein and OSA in children suggests that among obese male children, elevations in serum C-reactive protein precede the development of OSA.[80] However, even among youth without obesity, management of inflammation (eg, initiation of steroid, leukotriene inhibitors) may help to alleviate the severity of symptoms of OSA by reducing inflammation.[81] Adenotonsillectomy has also been shown to reduce levels of inflammation in children treated for OSA.[82]

CARDIOVASCULAR COMPLICATIONS OF SDB AND OSA

Inadequate sleep duration of <5 hours per night in children and adolescents has been linked to an increased risk of hypertension and is also associated with an increased prevalence of obesity.[50,83] Mild degrees of OSA (eg, AHI as low as 2 events/h) have been associated with unfavorable changes in the cardiometabolic health of youth.[84] Given that ≈30% to 60% of obese youth have OSA[84] and obesity is associated with hypertension in youth,[85] the question of whether OSA alone versus the comorbidity of obesity drives elevations in blood pressure (BP)

among children and adolescents with OSA remains to be determined.[83] Children with OSA are at greater risk for autonomic dysfunction, endothelial dysfunction, and ventricular remodeling.[46,86,87,88] OSA during childhood has also recently been shown to be an independent predictor of hypertension during adulthood.[89] However, 2 meta-analyses and a series of studies have reported opposing conclusions regarding the impact of OSA on BP.[90,91] Nevertheless, it is important to consider the potential role of OSA on risk for hypertension in children, given that hypertension is a primary risk factor for CVD that tracks from childhood into adulthood.[92,93]

OSA and Systemic Hypertension in Children and Adolescents

Hypertension is independently associated with SDB among adults in a dose-dependent manner with estimated OR of 2.89 (95% CI, 1.46–5.64) among adults with severe OSA (eg, AHI ≥15.0 events/h) according to in-office manual BP assessments.[94] However, given that OSA-associated hypertension is largely nocturnal, ambulatory BP monitoring may be a more accurate modality for diagnosing hypertension among adults with OSA.[95]

Among children and adolescents, a potential relationship between hypertension and OSA was first reported in 1976.[96] The relationship between BP and OSA is complex, regulated by activation of peripheral (eg, located within the carotid body) and central chemoreceptors (eg, located within the ventrolateral medullary surface of the brain stem) in response to hypoxia and increased CO_2 retention.[97] In response to the hypoxia and hypercapnia that occur secondary to airway obstruction, there is an increase in sympathetic nerve activation.[97] Hypoxia also stimulates the peripheral chemoreceptors, resulting in systemic vasoconstriction.[98] The result is elevation in systemic BP during episodes of apnea.[99] BP is also influenced by autonomic variability in children and adolescents. It has been proposed that the early stages of abnormal BP control may present with autonomic dysfunction in the form of increased sympathetic activity and decreased vagal tone, a change that is more likely to occur as children age.[100] Increased sympathetic activity during periods of apnea may contribute to the development of hypertension among children with OSA, but correlation between AHI and measured serum catecholamine levels is weak: noradrenaline: AHI r=0.36; adrenaline: AHI r=0.31.[101] In a large community sample, (eg, TuCASA [Tucson Children's Assessment of Sleep Apnea] study), elevations in systolic blood pressure (SBP) among children and adolescents with OSA were considered to be secondary to increased sympathetic vascular reactivity.[87,88,102]

Obesity and Systemic Hypertension in Children and Adolescents With OSA

It has been proposed that obesity, a condition known to be associated with higher BP, may explain the relationship between OSA and hypertension,[72,102,103] especially given the rising prevalence of childhood obesity.[83] Longitudinal studies, including data from the TuCASA study, suggest that independent of age or ethnicity (Hispanic compared with White), decreased sleep time and increased obesity are associated with increased BP among children 6 to 13 years of age.[12] The effects of OSA severity on BP may also be age dependent. Younger children 10 to 11 years of age with more severe OSA may have BP dysregulation, while older children develop higher sustained elevation in BP.[104] It is possible that obesity is a confounder for daytime elevations in BP that can be determined via in-office BP measurement, while nocturnal hypertension is less dependent on obesity status and more dependent on OSA severity.

Systemic Hypertension: Ambulatory BP Assessment

An AHI ≥5 events/h has been shown to be an independent risk factor for elevated SBP and diastolic blood pressure (DBP), even after adjusting for confounding factors such as increased BMI.[105] In a study by Li et al, among children 6 to 13 years of age, OSA was associated with nocturnal hypertension with an OR of 5.0 (95% CI, 2.0–12.7) for sleep SBP and an OR of 3.5 (95% CI, 1.5–8.1) for sleep DBP, respectively, compared with healthy controls.[106] In this same study and in a study published by Amin et al, however, there was no significant identified correlation between elevated daytime BP and OSA in children once analyses were adjusted for BMI.[104,106] Amin et al found that although there was greater BP variability, daytime BP was not higher.[104] In a separate cohort study of 96 children with reported snoring and high AHI (AHI >5 events/h) versus low AHI (AHI ≤5 events/h), BP recordings using ambulatory BP monitoring devices found that children with high AHI had higher wake SBP, sleep SBP, and sleep DBP. Children with higher wake SBP were more likely to be obese, while high sleep SBP and DBP were independent of obesity status. Increased oxygen desaturation index was a major contributor to the development of elevated sleep DBP.[72]

A normal response in BP during sleep is for the BP to drop by >10%, known as "nocturnal dipping." Children and adolescents with OSA have a limited (<10%) dip in BP while asleep (eg, less nocturnal dipping), consistent with abnormal BP regulation.[104] Children and adolescents with more severe OSA, as defined by an AHI >5 events/h, compared with children and adolescents with primary snoring, have less nocturnal SBP

dipping. Nocturnal dipping was 7.6% among children and adolescents with AHI >5 events/h versus 11.5% among children and adolescents with primary snoring (P<0.01).[105]

Manual and In-Office BP Assessment

According to data from the TuCASA study, elevated daytime SBP is associated with OSA (OR, 4.57; 95% CI, 1.21–17.3), while elevation in DBP is associated both with OSA (OR, 4.75; 95% CI, 1.22–18.5) and with obesity (OR, 4.57; 95% CI, 1.36–15.4).[102] In a study of 23 children and adolescents with adenotonsillar hyperplasia, SBP and DBP during REM sleep tended to correlate with AHI[107] such that higher SBP and DBP was associated with higher AHI. Elevations in daytime SBP and DBP among children with OSA may be dependent on obesity status.[102]

Despite observational and cohort study data, a large meta-analysis did not identify a relationship between SBP, DBP, and OSA in children and adolescents,[91] likely attributable to study heterogeneity. However, an updated meta-analysis revealed that OSA was associated with 3-to-1 greater odds of hypertension in children.[90] Additional studies demonstrate that the more severe the OSA, the more likely a child is to have high BP.[108]

Among normal-weight children, a relationship between OSA severity and SBP has also been observed. Normal-weight children and adolescents with AHI >5 events/h, have been shown to have higher BP compared with children and adolescents with an AHI of ≤1 event/h.[108] Similarly, among normal-weight children, there is an observed increase in sleeping SBP at baseline by OSA severity.[109] In conclusion, children with OSA appear to have higher BP than controls during both sleep and wake times, and BP levels increase with increasing severity of OSA.[106]

Cardiomyopathy and LVH

OSA is a major contributor to increased morbidity and mortality associated with CVD. The relationship between OSA and increased CVD risk is likely secondary to the proposed impact of OSA on ventricular mass.[110,111] Pathologic increase in left ventricular (LV) mass (eg, LVH) has been shown to be an independent risk factor for CVD that develops not only in response to the presence of comorbidities such as obesity and hypertension, but that may occur secondary to hypoxia, myocardial injury, and impaired nocturnal dipping (eg, normal decrease in BP while sleeping), occurring among persons with OSA, independent of hypertension. A cross-sectional study[112] evaluating the effect of OSA on LV mass in overweight/obese adolescents determined that children with OSA are more likely to have LVH (85.7% versus 59.4%; P=0.047). Furthermore, this same study determined that OSA was associated with 4 times greater odds of LVH (95% CI, 1.15–14.65; P=0.030) even after adjusting for age, sex, race, and BMI z-score. The odds of LVH among adolescents with severe OSA (AHI >10 events/h) were even greater. The described study demonstrated a 14:1 greater odds of LVH among youth with more severe OSA (95% CI, 1.14–172.64; P=0.039).[112] Amin et al[13] reported a similar result, finding that OSA was associated with at least an 11-fold increase in the risk for LVH in children (P<0.05), an association that was not demonstrated among children and adolescents with only primary snoring.

Among children and adolescents with known cardiomyopathy, OSA may result in worse cardiovascular-related outcome. In a prospective study of children and adolescents with cardiomyopathy, more than half of the children snored, and 48% had OSA. This study found that the median LV end diastolic volume index was significantly higher in children with OSA than in children without OSA (72.4 versus 54.0 mL/m^2; P=0.03).[113]

Right ventricular dimensions may also be negatively impacted by the presence of OSA. An AHI of >10 events/h is significantly associated with right ventricular (RV) dimension above the 95th percentile (OR, 6.7; 95% CI, 1.4–32; P<0.05).[13] Decreased RV systolic function, as measured by echocardiogram, has been reported among persons with OSA,[114,115] especially in the presence of complex disorders such as Down syndrome, Duchenne muscular dystrophy, and mucopolysaccharidoses.[16,116,117]

Treatment of OSA may result in improved LV wall thickness[118] and RV and LV systolic function.[114] Small cohort studies have demonstrated improved LV function and RV function in children and adolescents with moderate to severe OSA after adenotonsillectomy.[114,119] However, more research is needed to better elucidate the relationships between OSA and RV and LV structure, size, and function, as not all studies have consistently demonstrated a relationship between OSA and cardiac remodeling.[120]

Arrhythmia and OSA

In adults, OSA is associated with arrhythmia in at least 50% of patients.[21] Arrhythmias including atrial tachyarrhythmias (eg, atrial fibrillation),[121] ventricular tachyarrhythmias, bradyarrhythmias, prolongation of the QT interval,[122] and sudden cardiac arrest have been reported.[2,21,123] Adults with OSA are at particularly high risk for nocturnal arrhythmia according to

data from the DREAM (Determining Risk of Vascular Events by Apnea Monitoring) study. Even after adjusting for increased BMI, sex, and additional CVD risk factors (eg, angina, coronary artery disease, myocardial infarction, congestive heart failure, pacemaker, and history of coronary artery bypass grafting), the risk of nocturnal arrhythmia among people with OSA increased by 10% for every 10-unit increase in AHI (OR, 1.10; 95% CI, 1.04–1.15; P=0.0005).[124] Ventricular arrhythmias are more likely to occur during periods of apnea, but the mechanism mediating this response is uncertain.[21] The risk for bradycardia is thought to be attributable to the dive reflex that occurs after prolonged apnea and hypoxia.[21] Atrioventricular block and asystole have also been reported. Treatment of bradyarrhythmias under these circumstances includes treatment of OSA.[21]

OSA in adults has also been associated with poor response to antiarrhythmic medication use.[125] P-wave dispersion, the difference between maximum and minimum P-wave duration, as measured by ECG, is increased among adults with more severe OSA,[126] where P-wave dispersion reflects prolongation of intra- and interatrial conduction times in the remodeled atrium prone to atrial arrhythmia, including atrial fibrillation.[127,128] Among children and adolescents, there has been very little published regarding the relationship between OSA and arrhythmia. It has been proposed that hypoxemia, hypercapnia, changes in intrathoracic pressure, arousal, and sleep deprivation associated with OSA result in sympathetic activation, left atrial enlargement, and systemic inflammation, leading to an increased risk for arrhythmia.[123] QT dispersion may also be a precursor of ventricular arrhythmia among people with OSA.[129] In a study of 44 children 1 to 12 years of age with OSA, P-wave dispersion was most pronounced among youth with more severe OSA versus mild OSA or unaffected controls.[130] Higher QT dispersion, defined as the difference between the maximum and minimum QT interval, has also been associated with increased risk for ventricular arrhythmia and has been reported among children with more severe OSA.[129] Autonomic regulation of heart rate may be affected by OSA, such that higher heart rate variability has been investigated as a potential marker of more severe OSA. A small retrospective cohort of children with OSA (1993–1995) identified enhanced beat-to-beat (R-to-R) interval variation at lower heart rates and reduced variation at higher heart rates.[131,132] More recent studies have demonstrated that heart rate variability among youth with OSA may not vary with polysomnography-defined OSA severity.[133]

Obesity and MetS

Seventeen percent of children and adolescents have obesity, while 2% to 6% have severe obesity.[134,135] Numerous studies have demonstrated a linear relationship between sleep duration and BMI. A recently published meta-analysis has shown that for each fewer hour of sleep, the risk of overweight/obesity increases[136] and that children with shorter-than-recommended sleep duration have a 1.58 pooled odds for overweight/obesity (pooled OR, 1.58; 95% CI, 1.26–198, P<0.05) while children with shortest sleep duration have a 1.92 pooled odds for overweight/obesity.[137] OSA has also been associated with impaired glucose homeostasis.[107]

OSA severity may be improved with multidisciplinary weight reduction intervention.[138] Increased sleep duration may facilitate weight loss via increases in serum leptin levels (a hormone predominantly made by adipose cells and enterocytes in the small intestine that helps to regulate energy balance by inhibiting hunger).[139]

MetS is a strong risk factor for CVD and is associated with higher serum insulin levels, triglyceride levels, elevated BP, and lower high-density lipoprotein cholesterol levels. Severely obese children and adolescents are not only at risk for MetS, but have elevated AHI levels, lower nadir Sa_{O_2}, and other markers of more severe OSA.[84] The association between MetS and OSA in children is not limited to children with severe OSA, but MetS is also present in children with mild OSA (AHI ≥2 events/h). Evidence to support a relationship between MetS and OSA in children and adolescents is further compounded by findings that continuous positive airway pressure (CPAP), a treatment for OSA, appears to result in significant lowering of the serum triglyceride and low-density lipoprotein cholesterol levels and in improved high-density lipoprotein cholesterol levels.[140] Greater desaturation time (time during sleep when O_2 saturations are <90%) is associated with higher glycated hemoglobin values, even if these values are within the normal range.[107] Finally, OSA negatively impacts glycemic control in children with diabetes mellitus, just as it does in adults.[141] Treatment of OSA with adenotonsillectomy may lead to improved markers of MetS in youth, including insulin resistance, fasting glucose, serum triglyceride, and high-density lipoprotein cholesterol in the short term.[142] There may be no immediate change in inflammatory (C-reactive protein, circulating intercellular adhesion molecule-1) and metabolic marker (eg, insulin level) levels or in BP.[142] Obesity status may be the primary mediator of the relationship between OSA and insulin resistance.[48]

PULMONARY HYPERTENSION, COR PULMONALE, AND SDB

Hypoxia is an important influencer of pulmonary vasomotor tone and is a potent pulmonary vasoconstrictor. A relationship between hypertrophied tonsils and adenoids, upper airway obstruction causing hypoxia, pulmonary hypertension, and cor pulmonale was first proposed in 1965.[143,144] Current pediatric pulmonary hypertension guidelines recommend that if primary causes of pulmonary hypertension, such as lung disease and CHD, are ruled out, children and adolescents should undergo a sleep study.[145]

However, additional evidence suggests that the presence of pulmonary hypertension and the development of cor pulmonale may be less common in children and adolescents with OSA and, if present, secondary to other comorbid conditions.[16,146] A retrospective study of 2020 pediatric patients diagnosed with OSA in the San Antonio Military Health System found that the prevalence of pulmonary hypertension was low among children and adolescents with OSA (eg, 1.8%). This study also found that none of the patients with pulmonary hypertension had severe OSA and that all of the children with pulmonary hypertension had comorbid cardiac conditions.[146]

However, if a child develops sleep-dependent airway obstruction, early recognition and appropriate treatment with improved respiratory control leads to improved ventilation and elimination of asphyxia during sleep and thus a lower risk for pulmonary hypertension and cor pulmonale.[116] The presence of cor pulmonale once developed can be reversed by surgical removal of obstructing airway tissue.[117] In conclusion, although the deleterious effects of recurrent upper airway obstruction on pulmonary circulation may be physiologically intuitive, only a small number of studies have reported an association between OSA and pulmonary hypertension in children and adolescents.[16,115,147] The presence of pulmonary hypertension among children and adolescents with OSA may be more related to the severity and duration of hypoxia, the presence of hypercapnia, and the presence of acidosis rather than the absolute presence of airway obstruction leading to direct pulmonary vasoconstriction.[116,117] Additional studies are necessary to improve our understanding of how pulmonary circulatory pressures may be impacted by upper airway obstruction and whether there truly exists a causal link between OSA and pulmonary hypertension among children and adolescents. However, the greater risk is that of CVD and MetS among children with OSA.

TREATMENT AND OUTCOMES: INADEQUATE SLEEP DURATION, SDB, AND OSA

A detailed description of the treatment of OSA in youth is beyond the scope of this scientific statement, and at present there are no universally accepted criteria for initiation of treatment. Options for treatment of inadequate sleep duration, poor sleep efficiency, and OSA include behavioral, medical, and surgical intervention. Later school start times can improve sleep duration in adolescents,[148] and the AAP recommends that middle and high schools start after 8:30 AM.[149] Whether later school start times will result in improved cardiometabolic health in children is an area for future study.

Sleep habits that improve sleep quality and duration include consistent bedtime and wake times. Consistent and earlier bedtimes among younger children lead to decreased sleep onset latency and increased sleep duration, in both longitudinal and interventional studies.[150] Several small randomized controlled trials have shown that it is possible to improve sleep routines and sleep duration in children[151-153] and in adolescents[139,154,155,156] using educational interventions, phone- or text-based coaching, the provision of beds and bedding if children and adolescents lack adequate bedding. Two randomized controlled trials demonstrated that not only are such interventions associated with improved sleep hygiene but have also been associated with reductions in adiposity.[139,152] No randomized trials to date, however, have assessed the impact of such therapies on cardiovascular risk factors other than adiposity.

Over the past decade, treatment of OSA has been formalized with the recommendations encapsulated within the clinical guidelines of 3 societies: the AAP, the American Academy of Sleep Medicine, and the AAO–HNS.[18,38,50] The AAP, American Academy of Sleep Medicine, and AAO–HNS generally agree on adenotonsillectomy as the first line of treatment of upper airway obstruction, with multiple studies indicating relief of upper airway obstruction as measured by polysomnography as well as symptoms.[18] Watchful waiting is also suggested as a potential option for children with mild disease. The only randomized controlled trial comparing early adenotonsillectomy to watchful waiting in children 5 to 10 years of age, the CHAT (Childhood Adenotonsillectomy Trial), study found that surgery is superior in the domains of behavioral, quality-of-life, and symptom score outcomes.[77]

Today, symptoms of OSA are the principal indication for almost 500 000 children undergoing adenotonsillectomy in the United States. Otolaryngologists perform the procedure commonly in outpatient settings, and a recovery period of a few days is anticipated. The

most common serious complication related to the procedure is bleeding, which may occur immediately or in a delayed fashion in up to 5% of all children. The severity of OSA may predict the incidence of perioperative respiratory adverse events, which could be minimized by the administration of preoperative albuterol and the appropriate titration of perioperative anesthetic protocols.[157]

For children who are not candidates for adenotonsillectomy, CPAP therapy has been used and has been shown to be effective,[77] but adherence to recommended use remains a major barrier. For children, milder forms of OSA are usually not treated. The mechanism of CPAP-related benefit is related to the elimination of obstructive events by pneumatic stenting of the airway. Although CPAP has been shown to be efficacious and well tolerated in other studies, the principal limitation associated with its use has been compliance. Hawkins et al[158] showed that continuous adherence to CPAP therapy is suboptimal, although female sex and developmental delay are associated with better adherence. Although behavioral interventions may promote adherence, future investigations should focus on other pathways that could potentially improve adherence.

In children with persistent symptoms after adenotonsillectomy or when CPAP is considered as primary modality of treatment, surgical procedures to improve the upper airway may be of benefit. Investigations should focus on identification of the site of obstruction. A simple nasal examination aided by nasal endoscopy may identify a deviated septum, the correction of which may improve nasal airflow and facilitate better use of CPAP masks. Assessment of craniofacial anatomy may also provide surgical options such as distraction osteogenesis for mandibular retrognathia and maxillomandibular advancement to improve the airway at the level of the palate and tongue. Lingual tonsillectomy, tongue base reduction, and laryngeal procedures such as supraglottoplasty address anatomic obstruction at the level of the tongue base and the larynx. In children in whom the severity of obstruction has progressed to cardiopulmonary complications, or when other forms of treatment have failed, a tracheostomy may provide benefit.

Impact of Treatment of OSA on Cardiovascular Health

Adenotonsillectomy is highly effective from a procedural perspective; however, there is currently limited high-quality evidence of an improved cardiovascular profile after adenotonsillectomy.[114,142,159,160,161] Cardiovascular parameters improved by adenotonsillectomy include improvements in ventricular function,[114] BP,[160] and pulmonary artery pressure.[161] In a systematic review,[161] the majority of the 14 articles included in the study reported an improvement in cardiovascular parameters and OSA symptoms after surgery. The authors showed that 3 studies reported improvement in BP, 6 reported improvement in mean pulmonary artery pressure, 7 reported improvement in echocardiographic findings, and 1 reported a decrease in pulse rate and pulse rate variability after adenotonsillectomy. After adenotonsillectomy, 44 youth who underwent repeat polysomnography were found to have significantly lower overall DBP load (proportion of elevated readings) despite a significant increase in BMI.[162] However, adenotonsillectomy may have very little impact on ambulatory BP control in children and adolescents 4 to 16 years of age with OSA who have normal preoperative BP.[162-164] Obese children and adolescents may also be less likely to experience an improvement in BP with treatment of OSA if there is persistent airway obstruction.[18,165-167] Improvements in LV mass and wall thickness were not demonstrated in response to adenotonsillectomy.[159]

Children who undergo adenotonsillectomy may have symptoms of attention deficit hyperactivity disorder and daytime sleepiness, which respond well to surgery[168]; however, the lack of significant differences in the majority of outcomes in the long term between groups of children who undergo surgery and those who are managed conservatively may suggest the need to investigate better outcome measures to assess response to treatment. Furthermore, a consistent relationship between baseline symptoms and objective measures of upper airway obstruction such as AHI and oxygen desaturation index has not been observed, complicating the assessment for surgical candidacy of children who are evaluated with symptoms of OSA. Weight loss in obese or overweight children as an intervention for relief of airway obstruction has been shown to be procedurally effective, although concerns regarding compliance and long-term effectiveness have prevented its mainstream implementation. Children with comorbid conditions who are considered to be high risk on the basis of preoperative assessment for general anesthesia may be recommended alternate treatments. The use of intranasal corticosteroids with or without systemic anti-inflammatory agents may be considered suitable as first-line treatment for children with mild OSA in whom tonsillectomy is contraindicated. Intranasal corticosteroids may be more effective in younger, nonobese children. Nasal fluticasone or budesonide has been shown to reduce both the frequency and severity of obstructive events, specifically when the severity of OSA is mild to moderate on the basis of polysomnography assessments. In others, a combination therapy that includes oral leukotriene receptor antagonists may be efficacious, although they are generally deemed to be inferior in outcomes related to symptom relief.[169]

ANESTHESIA RISK AND PERIOPERATIVE CONSIDERATIONS IN SDB AND OSA

Children and adolescents with severe OSA require careful preoperative assessment and meticulous intra- and postoperative management.[20,23] Anesthetic agents should be carefully considered when managing children and adolescents with OSA, and attempts should be made to reduce opioid-associated respiratory depression.[20,23] Given that they are at risk for severe airway obstruction, including hypoxemia and hypercapnia, during and after surgery,[20] it is recommended that children with severe OSA, either clinically determined or if AHI >10 events/h, and children <3 years of age with significant comorbidities (eg, failure to thrive, obesity, cardiac involvement such as RV hypertrophy, trisomy 21, history of prematurity, craniofacial abnormalities, neuromuscular diseases, chronic lung disease, and SCD), be hospitalized for at least 23 hours after surgery.[170] Identification of children and adolescents with severe OSA requiring adenotonsillectomy and who are at greatest risk for adenotonsillectomy-related complications is particularly important.

In conclusion, OSA is common among children and adolescents. Children with severe OSA and children <3 years of age with significant comorbidities are at greater risk for severe and potentially life-threatening airway obstruction with anesthetic administration and immediately after surgery. Hospitalization for high-risk patients for the first 23 hours immediately after surgery is indicated.

Future Studies

To better understand the long-term CVD-related risk associated with the presence of OSA in childhood, additional well-designed longitudinal studies incorporating ambulatory blood pressure monitoring data and measures of metabolic disease (eg, lipid profile, glucose, and glycated hemoglobin levels) are needed over time. Also important are studies evaluating the relationship between OSA and noninvasive markers of CVD, including carotid intima media thickness and pulse wave velocity.

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*Modest.
†Significant.

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*Significant.

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