Adenotonsillectomy Outcomes in Treatment of Obstructive Sleep Apnea in Children

A Multicenter Retrospective Study

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***Rationale*: The overall efficacy of adenotonsillectomy (AT) in treatment of obstructive sleep apnea syndrome (OSAS) in children is unknown. Although success rates are likely lower than previously estimated, factors that promote incomplete resolution of OSAS after AT remain undefined.**

***Objectives*: To quantify the effect of demographic and clinical confounders known to impact the success of AT in treating OSAS.**

***Methods*: A multicenter collaborative retrospective review of all nocturnal polysomnograms performed both preoperatively and postoperatively on otherwise healthy children undergoing AT for the diagnosis of OSAS was conducted at six pediatric sleep centers in the United States and two in Europe. Multivariate generalized linear modeling was used to assess contributions of specific demographic factors on the post-AT obstructive apnea-hypopnea index (AHI).**

***Measurements and Main Results*: Data from 578 children (mean age, 6.9 $\pm$ 3.8 yr) were analyzed, of which approximately 50% of included children were obese. AT resulted in a significant AHI reduction from 18.2 $\pm$ 21.4 to 4.1 $\pm$ 6.4/hour total sleep time ($P < 0.001$). Of the 578 children, only 157 (27.2%) had complete resolution of OSAS (i.e., post-AT AHI $<$1/h total sleep time). Age and body mass index z-score emerged as the two principal factors contributing to post-AT AHI ($P < 0.001$), with modest contributions by the presence of asthma and magnitude of pre-AT AHI ($P < 0.05$) among nonobese children.**

***Conclusions*: AT leads to significant improvements in indices of sleep-disordered breathing in children. However, residual disease is present in a large proportion of children after AT, particularly among older ($>$7 yr) or obese children. In addition, the presence of severe OSAS in nonobese children or of chronic asthma warrants post-AT nocturnal polysomnography, in view of the higher risk for residual OSAS.**

Keywords: sleep apnea, obstructive; adenoidectomy; tonsillectomy; pediatrics

AT A GLANCE COMMENTARY

Scientific Knowledge on the Subject

The efficacy of adenotonsillectomy in the treatment of pediatric obstructive sleep apnea (OSA) has not been systematically explored.

What This Study Adds to the Field

Using a multicenter study design consisting of eight pediatric sleep centers across the United States and Europe that routinely conduct preoperative and postoperative nocturnal polysomnography, the outcomes of adenotonsillectomy for OSA in a large cohort of children were examined, and revealed a high frequency of residual OSA. Statistical modeling of specific risk factors allows for potential identification of children at risk for residual OSA, and may help in formulation of future management strategies.

Obstructive sleep apnea syndrome (OSAS), the most severe entity in the spectrum of sleep-disordered breathing, is a highly prevalent condition in children, affecting 2–3% of children (1–4). OSAS in children is characterized by recurrent periods of elevated upper airway resistance with partial or complete intermittent obstruction of the upper airway during sleep, and is usually accompanied by snoring, episodic oxyhemoglobin desaturation, hypercapnia, and repeated arousals. Habitual snoring, defined as occurring greater than or equal to 3 nights per week, and not associated with obstructive apneas, gas exchange abnormalities, or sleep fragmentation, has an even higher reported median prevalence of approximately 12% (5, 6). Although there is still continuing debate on the exact polysomnographic criteria that will effectively discriminate OSAS from habitual snoring, timely diagnosis and treatment of OSAS is of paramount importance, because this condition not only accounts for markedly increased health care costs (7), but is also associated with several morbidities, such as neurocognitive and behavioral disturbances (8, 9); enuresis (10); and cardiovascular dysfunction including systemic and pulmonary hypertension (11–13), ventricular remodeling (14), and endothelial dysfunction (15, 16).

Hypertrophy of adenotonsillar tissue is an undisputed major contributor to the development of OSAS in otherwise healthy children. Anatomic impingement of the upper airway by enlarged upper airway lymphoid tissues will increase pharyngeal resistance, and may ultimately result in the episodic airway narrowing and collapse that characterize OSAS (17, 18). However, not all children with adenotonsillar hypertrophy

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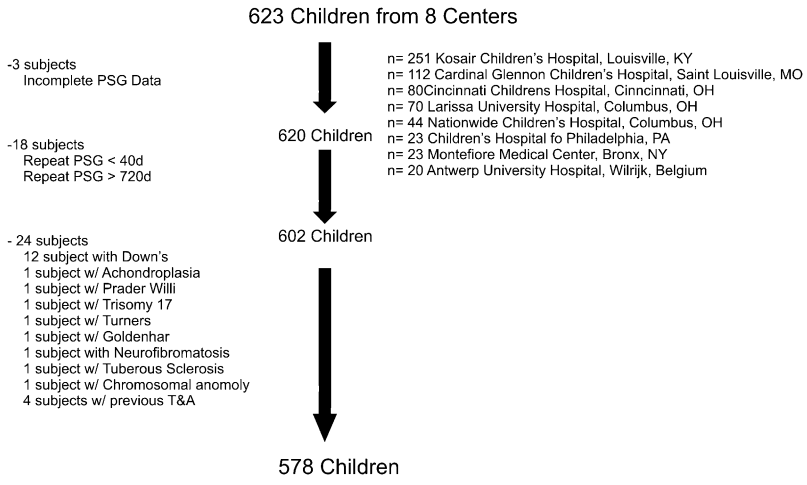

Figure 1. Summary of subject recruitment.

suffer from OSAS. Nevertheless, despite contributions by craniofacial structures, and by genetic and neuromuscular factors, the severity of OSAS has been associated, at least in part, with tonsillar and adenoidal size (19). Accordingly, the practice guidelines established by the American Academy of Pediatricians recommend adenotonsillectomy (AT) as the first line of treatment for childhood OSAS (20). In support of such approach, AT has been shown to lead to significant improvements in most cases of OSAS in children, as reported from several meta-analysis studies (21–23). However, there are few studies examining the overall efficacy and outcomes of AT in pediatric OSAS. Furthermore, there is a paucity of information on the factors that may contribute to the occurrence of residual OSAS post-AT. Thus, the present multicenter collaborative study aimed to delineate factors that may assist in the prediction of the clinical response to AT in children with OSAS through careful retrospective examination of available demographic and polysomnographic information on children who underwent overnight polysomnograms (PSG) before and after AT.

METHODS

Eight pediatric centers routinely performing nocturnal polysomnography on children participated in the study and polysomnographic data were available for 623 children who had sleep studies performed both before and after AT, as follows: Kosair Children's Hospital, Louisville, KY (n = 251); Cardinal Glennon Children's Hospital, Saint Louis, MO (n = 112); Cincinnati Children's Hospital, Cincinnati, OH (n = 80); Larissa University Hospital, Larissa, Greece (n = 70); Nationwide Children's Hospital, Columbus, OH (n = 44); Children's Hospital of Philadelphia, Philadelphia, PA (n = 23); Montefiore Medical Center, Bronx, NY (n = 23); and Antwerp University Hospital, Wilrijk, Belgium (n = 20). All six American sites were accredited by the American Academy of Sleep Medicine. The data collected from four of the eight sites included in the study represented prospective clinical routines of repeating overnight sleep studies after AT irrespective of patient history or symptoms, accounting for 513 children (82% of the data). Data collection commenced July 2007 and was terminated September 2008. For all eight centers, approval of the study by an Institutional Review Board or equivalent was obtained through a waiver of patient consent for this retrospective study.

Post-AT PSG deemed appropriate for analysis were those repeated greater than 40 days after the date of surgery (to minimize confounding effects of postoperative swelling and healing), and those less than 720 days, to minimize the effect of potential adenoidal regrowth.

All centers used a standardized datasheet template for patient chart data extraction that included specific demographic variables and polysomnography data. However, because of lack of standardization on patient charting procedures and sleep study reports, missing data points occurred. Each center's principal investigator defined data pertaining to ethnicity.

Body mass index (BMI) was calculated from measured height and weight in the records and BMI z-score was computed using Centers for Disease Control and Prevention 2000 growth standards (www.cdc.gov/growthcharts) and online software (www.cdc.gov/epiinfo). A BMI z-score greater than 1.65 (>95th percentile) was considered as fulfilling obese criteria. BMI data were collected at the time of the pre-AT and post-AT PSGs when available.

Of note, although variations in the conductance and scoring of nocturnal polysomnography among the eight centers were present, *post hoc* analysis of sleep study data was standardized as follows. The proportion of time spent in each sleep stage was expressed as a percentage of total sleep time (TST). Central, obstructive, and mixed apneic events were counted. Obstructive apneas are defined as the absence of airflow with continued chest wall and abdominal movement for duration of at least two breaths (24, 25). Hypopneas are defined as a decrease in oronasal flow of greater than or equal to 50% with a corresponding decrease in Spo_2 of 3% or more or EEG arousal (25, 26). The obstructive apnea hypopnea index (AHI) was defined as the number of obstructive apneas and hypopneas per hour of TST. Arousals were defined as recommended by the American Sleep Disorders Association Task Force report and included respiratory-

TABLE 1. DEMOGRAPHIC SUMMARY OF ALL CHILDREN UNDERGOING ADENOTONSILLECTOMY FOR OBSTRUCTIVE SLEEP APNEA SYNDROME

Number of subjects	578
Mean age, yr (n = 578)	6.9 ± 3.8
Age range	8 mo–18 yr
Number of males (n = 578)	355 (61.4%)
Mean body mass index z-score (n = 471)	1.35 ± 1.74
Number of obese children (body mass index z-score >1.65)	238 (50.6%)
Ethnicity (n = 551)	
White	332 (60.3%)
African American	127 (23%)
Hispanic	69 (12.5%)
Other	23 (4.2%)
Asthma (n = 459)	136 (29.6%)
Allergic rhinitis (n = 537)	212 (39.5%)
Family history of obstructive sleep apnea syndrome (n = 355)	105 (29.5%)
Prematurity (n = 413)	64 (15.5%)
Number of days between preadenotonsillectomy and postadenotonsillectomy polysomnograms	209 ± 125.9

Availability of demographic data from patient charts is revealed in parentheses. All data expressed as mean ± SD.

TABLE 2. POLYSOMNOGRAPHIC DATA IN ALL CHILDREN UNDERGOING ADENOTONSILLECTOMY FOR OBSTRUCTIVE SLEEP APNEA SYNDROME

Variable	Preadenotonsillectomy	Postadenotonsillectomy	*P* Value
Sleep efficiency, % (n = 397)	83.8 ± 11.2	85.5 ± 11	<0.001
Sleep onset latency, min (n = 393)	29.8 ± 38.3	27.4 ± 33.9	= 0.264
Number of awakenings, no. (n = 300)	12.9 ± 11	10.6 ± 8.2	<0.001
Wake after sleep onset, % of TST (n = 397)	13.4 ± 37.7	9.2 ± 11	= 0.113
REM onset latency, min (n = 371)	157.6 ± 97	155.7 ± 80.5	= 0.719
Stage 1 sleep, % of TST (n = 394)	6.8 ± 8	5.6 ± 5.2	= 0.002
Stage 2 sleep, % of TST (n = 394)	43.3 ± 12.5	45.8 ± 27.3	= 0.075
Stage 3 sleep, % of TST (n = 394)	7.8 ± 7.2	8.5 ± 11.2	= 0.151
Stage 4 sleep, % of TST (n = 394)	20.5 ± 9.9	21.5 ± 11.7	= 0.134
Stage REM sleep, % of TST (n = 507)	16.6 ± 7.4	16.8 ± 7.1	= 0.380
Total no. of obstructive hypopneas (n = 408)	90.7 ± 100.3	25.5 ± 38.8	<0.001
Total no. of obstructive apneas (n = 408)	37.9 ± 69.2	5.8 ± 20	<0.001
Apnea-hypopnea index, events/h TST (n = 578)	18.2 ± 21.4	4.1 ± 6.4	<0.001
Obstructive apnea index, events/h TST (n = 476)	6 ± 10.3	1.3 ± 4.4	<0.001
Total apnea index, events/h TST (n = 420)	6.7 ± 10.7	1.6 ± 3.3	<0.001
Respiratory arousal index, events/h TST (n = 173)	7.7 ± 8.1	2.4 ± 3	<0.001
Total arousal index, events/h TST (n = 285)	14.8 ± 16.2	9.8 ± 6	<0.001
Oxygen saturation nadir, % (n = 493)	80.2 ± 13.1	86.2 ± 8.3	<0.001

Definition of abbreviation: TST = total sleep time.
Availability of polysomnographic data from patient charts is revealed in parentheses. All data expressed as mean ± SD.

related (occurring immediately after an apnea, hypopnea, or snore) and spontaneous arousals. Arousals were expressed as the total number of arousals per hour of sleep time (26, 27).

Data Analysis

Because data from several centers were compiled, missing value analyses were performed, and the latter revealed no specific patterns. However, 18.7% pre-AT and 33% post-AT BMI z-scores of the total sample of 578 cases were missing. Therefore, these missing data points were substituted by a plausible value generated by regression-type analyses. In other words, missing data points were "filled in" by values generated from the original existing data points after 1,000 iterations. Imputation inferences are based on the observed data likelihood that links the observed data and the specified imputation model (i.e., "filled in" BMI z-score generation from age, AHI, time between PSG data, which were collected for each individual, and the existing BMI z-scores). Of note, subsequent comparison analyses resulted in no statistical discrepancies between the nonimputed and imputed BMI z-scores.

Descriptive statistics were performed by conventional statistical analysis. To level out the potential effect on AHI post-AT caused by the large spread in age and BMI z-score at the second PSG, we corrected the AHI post-AT for these potential confounders. This corrected AHI post-AT (post-AT AHI, hereafter) is the dependent variable in our generalized linear modeling (GLZ; with normal distribution, log link function). GLZ is a generalization of the regression model for dependent variables, which are linearly or nonlinearly related to the independent variables. The Wald statistic and residual analysis express the fit of the model. All analyses were performed with StatSoft (2008; STATISTICA data analysis software system, version 8.0., www.statsoft.com).

TABLE 3. SUMMARY OF DEMOGRAPHIC FACTORS INFLUENCING PREDICTING POSTADENOTONSILLECTOMY APNEA–HYPOPNEA INDEX

	Wald Statistic	*P* Value
Age	14,400	<0.001
Body mass index z-score	1,905	<0.001
Asthma	6	0.017
Preadenotonsillectomy apnea-hypopnea index	4	0.041
Sex	3	0.106
Allergic rhinitis	0	0.520
Ethnicity	0	0.793

RESULTS

Of the 623 children, data on 45 subjects were excluded, leaving a total of 578 (Figure 1). Reasons for exclusions included the following: five children had nocturnal polysomnographic studies performed less than 30 days after AT, whereas 13 children had sleep studies more than 720 days after AT. An additional four children were excluded because of repeated AT. Twenty children were excluded because of underlying exclusionary medical conditions, namely Down syndrome (n = 12); achondroplasia (n = 1); Prader-Willi syndrome (n = 1); trisomy-17 mosaic (n = 1); Turner syndrome (n = 1); Goldenhar syndrome (n = 1); neurofibromatosis type-1 (n = 1); and tuberous sclerosis (n = 1). Finally, three subjects were excluded because of missing polysomnographic data. All children undergoing PSG and AT were for symptoms and treatment of OSAS, respectively.

A summary of the pertinent demographic information for all children who were included in the final analysis is provided in Table 1. Although age ranged from 8 months to 18 years, the mean age of the cohort was 6.9 ± 3.8 years, and 528 (91.3%) of the 578 children were less than 13 years old. BMI information was available for only 471 children, among whom 50.6% fulfilled obesity criteria. Demographic data pertaining to ethnicity were available in 551 children, and revealed that most of the children (60.3%) were white.

Post-AT sleep studies were associated with significant improvements in the major indices of sleep architecture, with significantly fewer numbers of nighttime awakenings and significant improvements in sleep efficiency, although no significant differences were seen in percent of REM stage during sleep (Table 2). Similarly, significant improvements were seen in all major respiratory indices, including obstructive AHI, total

TABLE 4. INFLUENCE OF DEMOGRAPHIC FACTORS IN OBESE CHILDREN

	Wald Statistic	*P* Value
Age	9,574	<0.001
Body mass index z-score	358	<0.001
Asthma	0.1	0.809
Preadenotonsillectomy apnea-hypopnea index	0.2	0.651

Body mass index z-score >1.65.

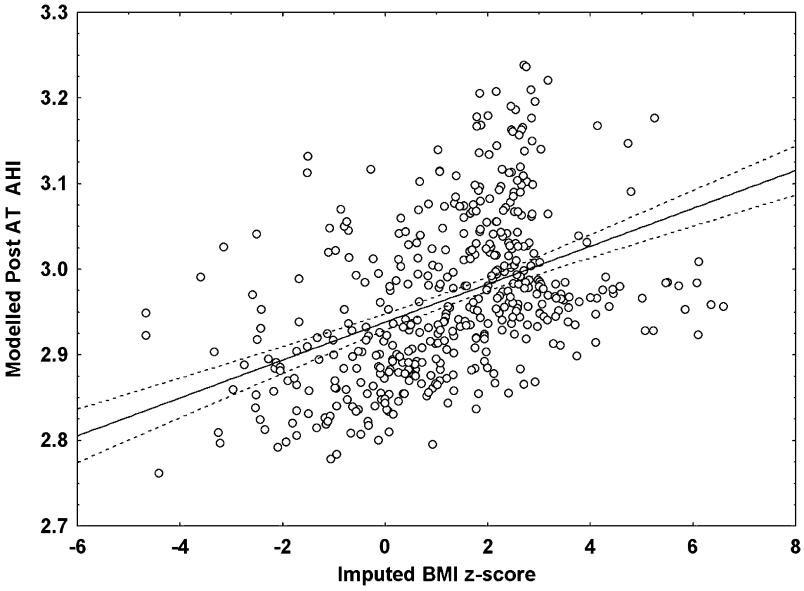

Figure 2. Correlation of body mass index z-score and predicted postadenotonsillectomy apnea-hypopnea index. AHI = apnea-hypopnea index; AT = adenotonsillectomy; BMI = body mass index.

number of obstructive events, respiratory arousal index, and nadir oxygen saturation. Of the 578 children, AT resulted in a reduction in AHI in 521 children (90.1%). Despite such improvements, the mean obstructive AHI improved from a pre-AT AHI of 18.2 ± 21.4/hour to a post-AT AHI of 4.1 ± 6.4/hour; the nadir oxygen saturation nadir was 86.1 ± 8.4% (i.e., well beyond the boundaries of normative published data) (25, 28). Using an obstructive AHI less than 1/hour TST as the cut-off, we found that only 157 children (27.2%) actually normalized their breathing patterns during sleep. Furthermore, 125 children (21.6%) had a post-AT AHI greater than 5/hour TST, clearly within the universally accepted criteria for OSAS.

Using GLZ we analyzed the predictive value of age, (imputed) BMI z-score, asthma, AHI pre-AT, sex, time elapsed from AT to post-AT PSG, allergic rhinitis, and ethnicity toward the corrected AHI post-AT. Through careful control of all significant variables, prediction of a post-AT in every child is achieved (goodness of fit: Pearson chi square = 0.096; $P < 0.001$), revealing that the factors most significantly associated with elevation of post-AT AHI in order of influence were advancing age (>7 yr); increasing BMI z-score; presence of asthma; and high severity of pre-AT AHI. No significant interaction effects among predictors emerged (Table 3). Subgroup analysis in obese and nonobese children using the GLZ model showed that the severity of OSAS (pre-AT AHI) and presence of asthma did not exert a significant influence in obese children, in contrast to the significant effect identified in nonobese children (Tables 4 and 5).

As shown in Figure 2, the correlation between BMI z-score and corrected post-AT AHI is significant ($r = 0.44$; $P < 0.05$). Furthermore, when examining the distribution of responses to AT, it becomes apparent that most children who exhibited residual OSAS after AT (i.e., post-AT AHI >5 events/h TST) also fulfilled obesity criteria with 59% of children with post-AT AHI greater than 5 events/hour TST meeting obesity criteria (BMI z-score >1.65).

Neither sex nor the presence of allergic rhinitis, prematurity, and family history modified the predicted post-AT AHI. However, the effect of pre-AT AHI (i.e., the severity of underlying OSAS at diagnosis) was significant, even if its relative contribution to the post-AHI prediction was small compared with those of BMI z-score and age. Notwithstanding, the unadjusted effect of pre-AT AHI on post-AT AHI was apparent, particularly among nonobese children (Figures 3 and 4). To examine the reliability of the model in the prediction of post-AT AHI, a Bland-Altman analysis was conducted and is shown in Figure 5.

TABLE 5. INFLUENCE OF DEMOGRAPHIC FACTORS IN NONOBESE CHILDREN

	Wald Statistic	*P* Value
Age	4,870	<0.001
Body mass index z-score	315	<0.001
Asthma	8	0.006
Preadenotonsillectomy apnea-hypopnea index	6	0.015

Body mass index z-score ≤1.65.

DISCUSSION

In this multicenter retrospective study, we show that when objective criteria, such as overnight PSG, are used to evaluate the efficacy of AT in children with OSAS, the success rate is well below previous expectations. Although the debate on the role of both presurgical and postsurgical nocturnal PSG in the

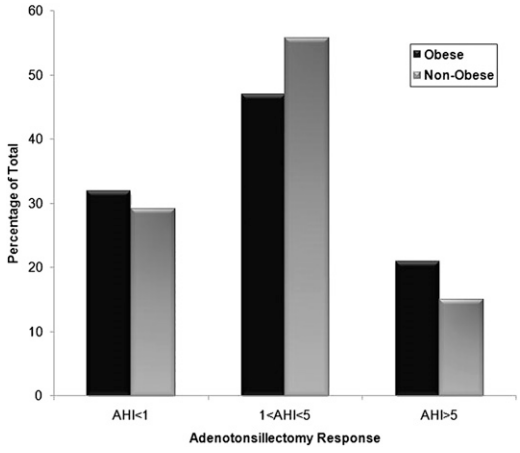

Figure 3. Distribution of response to adenotonsillectomy in obese and nonobese children.

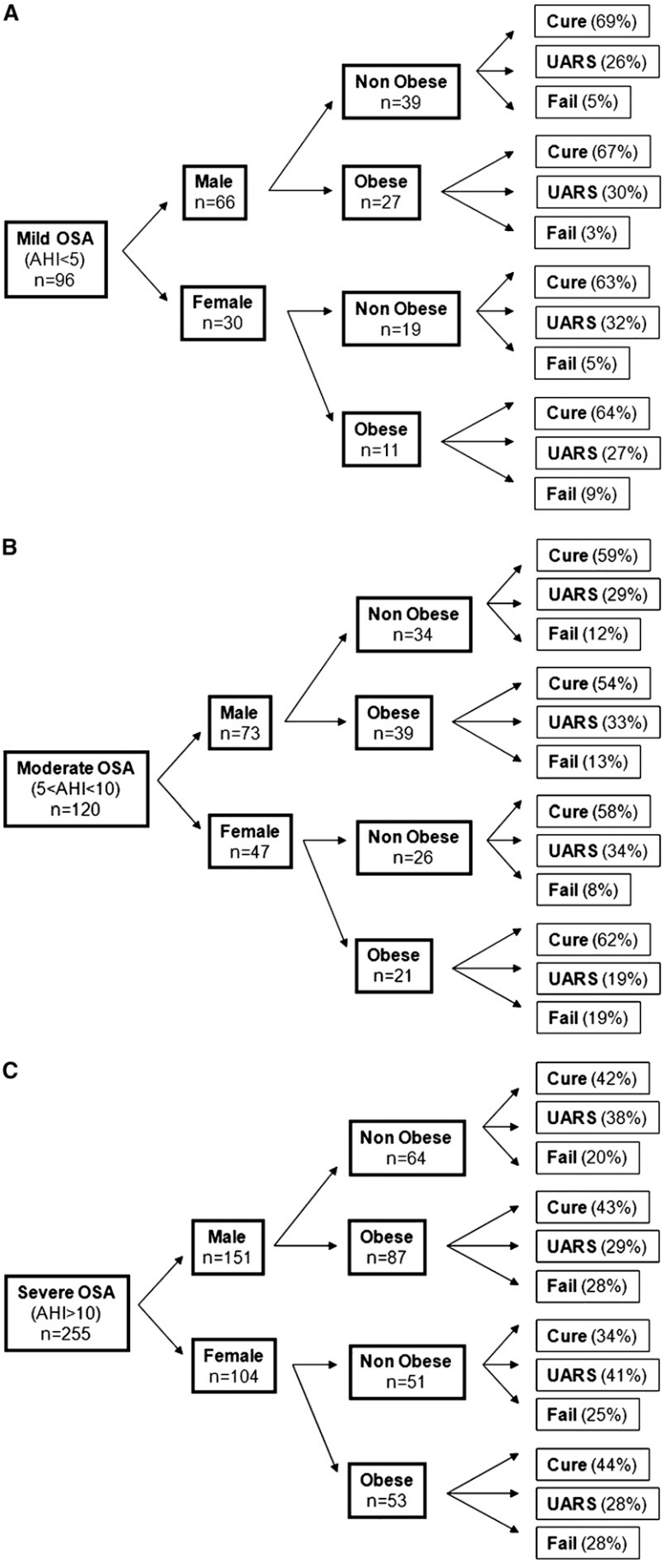

Figure 4. The effect of severity of obstructive sleep apnea (OSA) syndrome in predicting response to adenotonsillectomy (AT). (*A*) Mild OSA; (*B*) Moderate OSA; (*C*) Severe OSA. Cure = post-AT apnea-hypopnea index (AHI) < 1/hr; Mild sleep disordered breathing (mSDB) = 1/hr < post-AT AHI < 5/hr; Fail = post-AT AHI > 5/hr.

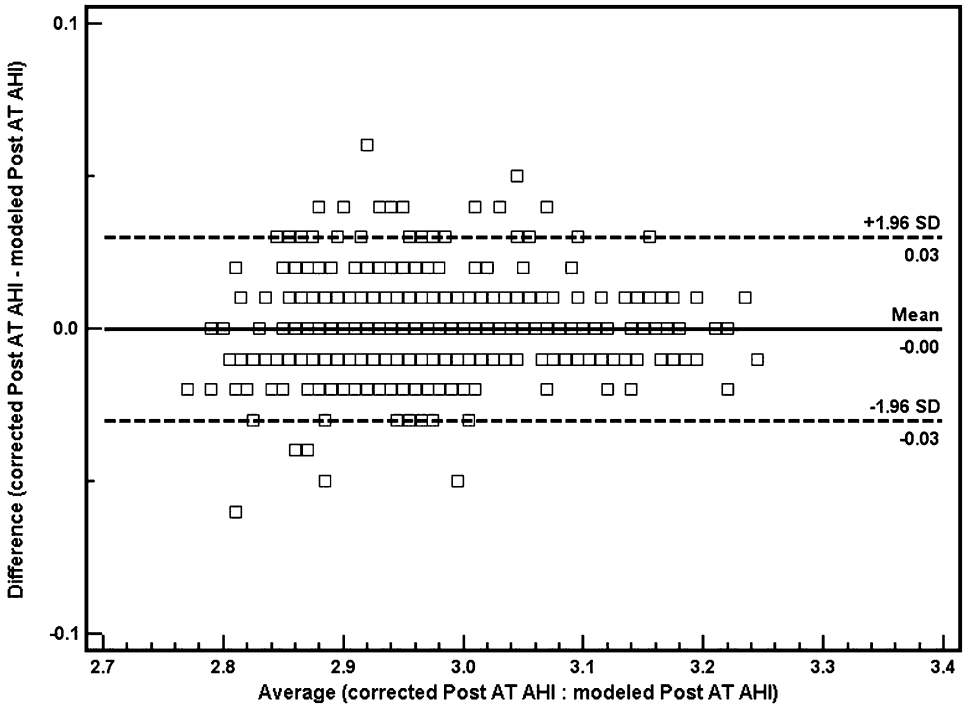

Figure 5. Bland-Altman analysis determining reliability of the model to predict postadenotonsillectomy apnea–hypopnea index (post AT AHI).

management of children with suspected sleep-disordered breathing (29, 30) is unlikely to be resolved any time soon, our previous findings in 110 consecutive children (31), the current findings on 578 children, and the findings reported in recent meta-analyses (21–23) provide compelling evidence that AT is not uniformly effective in curing OSAS in children, and that in the context of increasing obesity rates in children, the ability of AT to eradicate OSAS needs to be viewed with great skepticism (32).

The relatively large cohort included in the present study enabled critical assessment as to the predictability of residual OSAS after AT. In our generalized linear model, age and BMI z-score emerged as the strongest predictors. In particular for residual OSAS, after careful correction of all underlying confounders, older children and obese children were least likely to respond to AT. These findings should enable clinicians to make judicious use of nocturnal PSG after AT.

Previous studies (31–34) have shown that the severity of underlying OSAS, as determined by the pre-AT AHI, affected the surgical response, although the effect was remarkably small compared with those of age and BMI z-score and was applicable only to the nonobese children. In addition, and to the best of our knowledge, this is the first study to show that the presence of asthma contributes to an increased risk of persistent sleep-disordered breathing post-AT, particularly among nonobese children.

Although several studies have advocated for judicious use of presurgical nocturnal PSG as a means of predicting postsurgical AHI and conversely others have advocated that the nocturnal PSG is superfluous (29, 30), current findings would clearly be aligned with the first group. Indeed, the nocturnal PSG before AT would enable identification of children with primary snoring and treatment of only those children with OSAS in whom AT would be indicated. Furthermore, the PSG would also identify children with mild OSAS in whom the favorable responses to antiinflammatory therapies may obviate the need for AT (35–37). Finally, presurgical AT has been suggested to be necessary in guiding the intraoperative and postoperative management in children undergoing AT (38, 39). Regarding the need for a nocturnal PSG after AT, the current study would advocate for at least judicious implementation of post-AT nocturnal polysomnography. Indeed, although only 27.2% of children normalized their respiratory patterns during sleep as determined by the post-AT PSG, most children had evidence of residual sleep-disordered breathing. Furthermore, indications for administration of antiinflammatory agents when residual OSAS is mild (40) and of course adequate selection of those children needing initiation of continuous positive airway pressure would only be possible by post-AT PSG. More pragmatically, our findings would imply that in children undergoing AT for treatment of OSAS, children who are older, or obese, or nonobese children with asthma or with severe underlying OSAS should all *a priori* undergo postoperative nocturnal PSG after AT.

Some limitations merit discussion. The retrospective design of this study somewhat hampers the validity of recommendations until the results of a carefully conducted, prospective randomized study become available. In the current study, although most of the participating centers advocate for routine post-AT PSG, it is unclear whether similar criteria for such studies were indeed operational, and as such, a skewed population toward increased post-AT nocturnal PSG abnormalities may have occurred particularly if centers selected to repeat PSG in children who were clinically suspected to have residual OSAS. However, we should emphasize that this was not the case among 82% of the subjects.

Several study strengths are worthy of mention. First, this study is the first of its kind multicenter study to examine pre-AT and post-AT nocturnal polysomnography. This multicenter study design yields a very large sample size allowing for the use of a multilogistical regressional model thereby incorporating a large number of confounding factors in predicting surgical response. As shown in the Bland-Altman plot analysis (Figure 5), this model quite effectively predicted the primary study outcome (i.e., postsurgical AHI). Furthermore, the multicenter design most likely improves the generalizability of the study findings. Indeed, the current status of pediatric sleep research draws on a multitude of varying and somewhat conflicting opinions of diagnosis and treatment. The eight centers in this

study used various methods of conducting nocturnal PSG, used different software to score studies, and also were likely to implement relatively different criteria while scoring events in the PSG record. Intentionally, no interscore reliability was ascertained in this study to incorporate best the real-life diversity in the practice of pediatric sleep medicine across centers. In addition, one would assume that different surgical indications and operative techniques also existed among the eight centers. Application of a multicenter study design attempted to incorporate current practice variations, thereby establishing external validity in the study conclusions. Of course, the uneven distribution of sample size among the various centers may bias the outcomes and more pronouncedly reflect findings originating from centers that contributed larger numbers of subjects.

Notwithstanding the aforementioned considerations, our study suggests that AT is associated with significant improvements in sleep-disordered breathing in most children. However, older children, obese children, and nonobese children with either severe OSAS or with asthma are at an increased risk for residual OSAS. Under such circumstances and until the results of prospective multicenter studies become available, pre-AT and post-AT sleep studies should be conducted, at least among the high-risk groups identified herein.

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