Growth Velocity Predicts Recurrence of Sleep-disordered Breathing 1 Year after Adenotonsillectomy

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***Rationale*: Adenotonsillectomy, the first line of treatment of sleep-disordered breathing (SDB), is the most commonly performed pediatric surgery. Predictors of the recurrence of SDB after adenotonsillectomy and its impact on cardiovascular risk factors have not been identified.**

***Objectives*: Demonstrate that gain velocity in body mass index (BMI) defined as unit increase in BMI/year confers an independent risk for the recurrence of SDB 1 year after adenotonsillectomy.**

***Methods*: Children with SDB and hypertrophy of the tonsils and a comparison group of healthy children were followed prospectively for 1 year.**

***Measurements and Main Results*: Serial polysomnographies, BMI, and blood pressure were obtained before adenotonsillectomy and 6 weeks, 6 months, and 1 year postoperatively. Gain velocity in BMI, BMI and being African American (odds ratios, 4–6/unit change/yr; 1.4/unit and 15, respectively) provided equal amounts of predictive power to the risk of recurrence of SDB. In the group that experienced recurrence, systolic blood pressure at 1 year was higher than at baseline and higher than in children who did not experience recurrence.**

***Conclusions*: Three clinical parameters confer independent increased risk for high recurrence of SDB after adenotonsillectomy: gain velocity in BMI, obesity, and being African American. A long-term follow-up of children with SDB and monitoring of gain velocity in BMI are essential to identifying children at risk for recurrence of SDB and in turn at risk for hypertension.**

Keywords: growth velocity; adenotonsillectomy; sleep-disordered breathing

One of the most frequently encountered conditions associated with obesity is sleep-disordered breathing (SDB). In adults, the risk of SDB increases by 1.14 for every unit increase in body mass index (BMI) (1). In the pediatric population, the risk for developing SDB is fourfold greater in obese children than in children who are not obese (2). Although the prevalence of SDB in all children is believed to range from 2 to 3% (3–5), the prevalence in adolescents who are morbidly obese exceeds 50% (6, 7). Obesity is therefore strongly associated with abnormal upper airway control during sleep across all age groups.

Adenotonsillectomy, the first line of treatment in the management of childhood SDB, is the most commonly performed surgical procedure in children. The annual rate of adenotonsillectomy in children aged 0 to 14 years ranges from 19 per 10,000 in Canada to 115 per 10,000 in the Netherlands (8). At least half of these procedures are performed to relieve symptoms of SDB. In the first few weeks after adenotonsillectomy, obese children with SDB have a less favorable response to surgery than lean children. However, neither the long-term outcome nor the factors that contribute to recurrence of the disorder after adenotonsillectomy are clearly understood. Moreover, the impact of recurrence of SDB on important cardiovascular risk factors, such as blood pressure (BP), has never been examined.

AT A GLANCE COMMENTARY

Scientific Knowledge on the Subject

The current practice is to treat children with sleep-disordered breathing (SDB) by adenotonsillectomy without clear guidelines for postoperative follow-up to assess recurrence.

What This Study Adds to the Field

Three clinical parameters confer independent increased risk for high recurrence of SDB after adenotonsillectomy: gain velocity in BMI, obesity, and being African American. Rapid body mass index gain is an independent risk for recurrence after adenotonsillectomy. Recurrence is associated with an increase in blood pressure that is independent of body mass index.

Research investigating the relationship between adiposity and SDB has thus far focused on mechanical disease mechanisms, such as the volume of parapharyngeal and abdominal fat (9–11). These disease mechanisms do not, however, fully explain the absence of SDB in approximately half of children with morbid obesity. It also remains unclear why for the same level of obesity some children have recurrence of SDB after adenotonsillectomy whereas others have normal respiratory patterns.

Obesity is associated with an increase in endocrine and inflammatory activities of fat cells, many of which may modulate respiratory control (12–14). Several studies have demonstrated that the inflammatory consequences of obesity and its cardiovascular morbidity are influenced by the rate of weight gain over time independent of actual weight (15–19). Thus, the degree of adiposity and rate of weight gain may reflect different disease processes (20, 21). Together, these disease processes contribute to the overall obesity-related morbidity.

In this study, we sought to determine the 1-year recurrence of SDB in children after adenotonsillectomy and its impact on blood pressure. We investigated a novel construct, where two different measures of growth, BMI and gain velocity in BMI, might have independent effects on upper airway control during sleep. We tested the hypothesis that, independent of the degree of obesity, the rate of gain in BMI increases the risk of recurrence of SDB, which in turn contributes to elevation of BP 1 year after treatment by adenotonsillectomy.

METHODS

Design and Study Population

This prospective study recruited healthy children with adenotonsillar hypertrophy, in whom a predetermined need for adenotonsillectomy to

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treat symptoms of SDB had been made by their otolaryngologist before enrollment in the study. Children were evaluated at four time points: before undergoing adenotonsillectomy, and 6 weeks, 6 months, and 1 year after adenotonsillectomy. At each time point, they underwent polysomnographic evaluation and physical examination, which included documentation of weight, height, BP, and BMI.

Healthy children matched for age and sex were enrolled as a comparison group. The reasons for studying a group of healthy children were as follows: (*1*) to derive a cutoff for recurrence of SDB at 1 year defined as the level of apnea–hypopnea index (AHI) that exceeds by 1 SD the average AHI measured from the comparison group and (*2*) to determine the trend and variability of AHI over the duration of the study. Children in this group were monitored for 1 year and received three 6-month evaluations. The protocol was approved by the Cincinnati Children's Hospital institutional review board. Informed consent was obtained from the parents or legal guardian of each child, and assent was obtained from children older than 7 years.

Subjects

Children ranging in age from 7 to 13 years with nightly snoring and hypertrophy of the tonsils and adenoids were prospectively recruited for this study. Inclusion criteria for children with SDB were as follows: (*1*) an agreed upon decision between the otolaryngologist and the child's parents to undergo adenotonsillectomy to treat symptoms of obstructive breathing during sleep and (*2*) a polysomnogram consistent with the diagnosis of SDB. The comparison group consisted of age- and sex-matched healthy children without history of obstructive breathing during sleep. To retain children in the comparison group, their polysomnogram should have been without evidence of SDB or alveolar hypoventilation during sleep. Exclusion criteria for both groups were the presence of chronic medical conditions and genetic syndromes as determined by history and physical examination.

Polysomnography

Polysomnography studies were performed overnight according to the American Thoracic Society standards (22, 23), using computerized systems (Telefactor; Grass, West Warwick, RI). The interpretation of polysomnography was performed by an investigator (R.A.) who was blinded as to which group subjects were enrolled in, their medical and demographic characteristics, and the time sequence of the study. All investigators including the otolaryngologist were blinded to the results of the study. However, results were communicated to the managing otolaryngologist only when baseline AHI was 15 events or more per hour. This level of AHI was used by the managing otolaryngologist as an indication to perform the surgery at the main campus of the Cincinnati Children's Hospital rather than in a satellite facility and to admit the child postoperatively for overnight observation.

SDB was defined as an obstructive AHI of more than 1 event per hour of sleep. The recurrence of SDB was defined as an AHI of 3 events or more per hour of sleep. This level was derived from the comparison group population by calculating the level that exceeded by 1 SD the mean value of the comparison group at 1 year.

BP and BMI Slope Measurements

BP measurements were the average of three readings obtained after a minimum rest period of 5 minutes with the subjects in the sitting position. BP was measured before and 6 and 12 months after adenotonsillectomy. BMI gain velocity for the SDB group was calculated using BMI from the four visits as the slope of a linear regression line predicting BMI from time at baseline, scaled as change in BMI per year. BMI slope for the comparison group was derived from three time points.

Statistical Analysis

Exact tests were used to measure differences between the SDB groups in rates for dichotomous variables. Differences in AHI levels were tested with the Wilcoxon nonparametric test, whereas differences in age, BMI, and BP were tested with *t* tests. Comparisons between two time points within the SDB group for BP were performed by paired *t* tests. A two-tailed *P* value of less than 0.05 indicated statistical significance for all tests.

Three sets of multivariable logistic models predicting an AHI of 3 or more at the 1-year follow-up were constructed. The independent variables common to all models included age, sex, race, and BMI slope. The three sets of models differed in whether BMI at baseline, BMI at 1 year, or a mean BMI was entered into the model. In each of the models, all possible two-way interactions between either BMI variables or any of the demographic covariates were examined. All *P* values and confidence intervals derived from these logistic regressions were likelihood based. For each model, the C-statistic, or area under the receiver operating characteristic curve, was noted. Reduced models were estimated by removing one predictor at a time from the full model, and noting the c-statistics. C-statistics for the reduced models were compared to assess the relative contributions of different predictors to the overall predictive power of the full model.

A model that included age, race, BMI, and AHI at 1 year was constructed to predict the final systolic and diastolic BP.

RESULTS

Ninety-seven children, 62 with SDB and 35 in the comparison group, were enrolled in the study. After the initial evaluation, 22 children with SDB and 5 control subjects elected to withdraw from the study. A comparison of age, sex, race, BMI, AHI, and systolic and diastolic BP showed only a higher diastolic BP (62 ± 8 vs. 55 ± 5 mm Hg, $P = 0.03$) in children with SDB who completed the study compared with those who withdrew. Children in the comparison group who completed the study had a higher BMI (19 ± 4 vs. 16 ± 2, $P = 0.03$) compared with those who withdrew. Seventy children completed the whole protocol. Forty met the inclusion/exclusion criteria for SDB and 30 made up the comparison group. Eighteen of 40 children with SDB and 3 of 30 in the comparison group had a BMI greater than the 95th percentile at baseline. Half the SDB group had an AHI more than 3 at the 1-year evaluation (Table 1). Among those who had an AHI

TABLE 1. DEMOGRAPHIC AND POLYSOMNOGRAPHIC CHARACTERISTICS OF STUDY POPULATION

	Comparison Group (*n = 30*)	SDB, 1 yr AHI < 3 (*n = 20*)	SDB, 1 yr AHI > 3 (*n = 20*)
Age at baseline, yr	10.2 (2.2)	9.3 (2.1)	10.3 (2.2)
Age at 1-yr follow-up, yr	11.3 (2.2)	10.5 (2.1)	11.4 (2.2)
Male sex, %	40	65	55
African-American race, %	20	25	45
AHI, baseline	0.26 (0.28)	3.6 (3.2)	14.7 (18.3)*
BMI, baseline	18.7 (3.8)	19.2 (4.6)	25.0 (5.7)*
BMI > 95th percentile at baseline, %	10	20	70*
BMI regression slope	0.80 (0.99)	0.99 (1.20)	2.12 (1.38)*
Systolic BP, baseline	101 (10)	105 (11)	110 (14)
Diastolic BP, baseline	57 (9)	59 (8)	64 (7)†

Definition of abbreviations: AHI = apnea hypopnea index; BMI = body mass index; BP = blood pressure; SDB = sleep-disordered breathing.

Demographic and polysomnographic characteristics of study population expressed as frequencies and means ± SD.

* For comparisons between the two SDB groups, $P < 0.01$.

† $P < 0.05$.

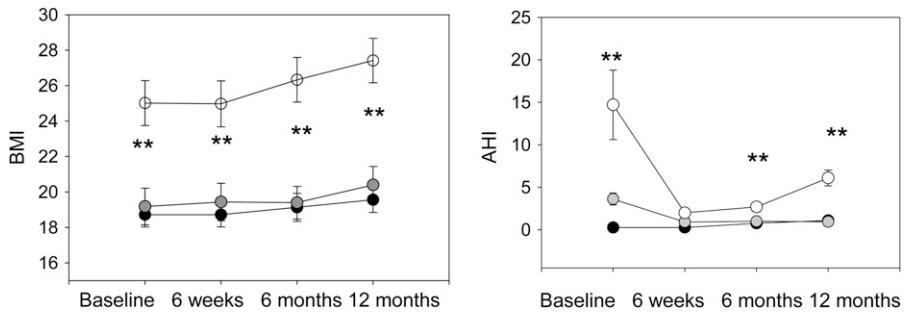

Figure 1. Serial changes, from baseline to the end of the follow-up period, in mean body mass index (BMI) and mean apnea–hypopnea index (AHI) by group. Groups were divided as comparison group and two sleep-disordered breathing (SDB) groups, one with an AHI less than 3 and one with an AHI greater than 3 at 1 year after adenotonsillectomy. n = 30 for the comparison group and n = 20 for each SDB group. For comparisons between the two SDB groups, $^{**}P < 0.01$. *Solid circles,* control group; *shaded circles,* AHI < 3 group; *open circles,* AHI > 3 group.

greater than 3 at 1 year, six (30%) had an AHI higher than their baseline value. In the same time period, 2 of the 30 children (7%) in the comparison group developed SDB, one child was obese and one nonobese.

Change in AHI after Adenotonsillectomy

The AHI of children with SDB decreased significantly from a mean of 9.2 ± 14 at baseline to 1.4 ± 2 at 6 weeks after surgery ($P \leqslant 0.001$). There was no difference in AHI measured at 6 weeks between those who ultimately had recurrence of SDB after 1 year and those who did not (Figure 1). The 6-week AHI showed no correlation with the AHI measured preoperatively or the AHI measured at 6 months and 1 year after surgery.

In the period from 6 months to 1 year postoperatively, both obese and nonobese children showed a trend toward increasing AHI over time (Table 2). A positive correlation was measured between preoperative AHI and that measured at 6 months ($r = 0.5$, $P < 0.01$) and 1 year ($r = 0.5$, $P < 0.01$) after surgery. These results suggest that preoperative polysomnography findings predict the 1-year outcome of surgery regardless of the short-term improvement seen at the 6-week postoperative time point.

Characteristics of Children Who Had Recurrence of SDB 1 Year after Adenotonsillectomy

Children with an AHI of 3 or more at 1 year were more likely to have an accelerated BMI gain, to be more obese, to be African American, and to have more severe SDB at baseline (Table 1). The rate of BMI gain, measured as BMI regression slope, was significantly larger in children with recurrence versus those without recurrence of SBD (Table 1).

Multivariable Logistic Regression

The independent effect of the BMI regression slope on the risk of SDB recurrence after adenotonsillectomy was demonstrated through multivariable logistic regression (Table 3). There were no significant two-way interactions between predictors in any of the models predicting SDB recurrence. Whether the assessment of BMI in the model was that from baseline, at 1 year, or from a mean BMI over 1 year, recurrence was significantly predicted by African-American race, BMI, and the BMI slope (Table 3). These same variables were significant predictors when the nonsignificant variables, age and sex, were removed (results not shown). The c-statistics for the reduced models suggest that race, BMI, and BMI gain provided roughly equal amounts of predictive power to the models. Odds ratios for SDB recurrence, adjusted for other variables in the models, were approximately 1.4 for each unit of BMI, 4 to 6 for each unit of BMI change per year, and 15 for African-American race (Table 3). These results demonstrate the independent effect of rate of BMI gain on the long-term risk for recurrence of SDB after adenotonsillectomy.

TABLE 2. NUMBER AND PERCENTAGE OF OBESE AND NONOBESE CHILDREN WITH AN APNEA–HYPOPNEA INDEX MORE THAN 3 PER HOUR OF SLEEP AT EACH TIME POINT DURING THE STUDY

	SDB ($n = 40$)		
	Nonobese = 22	Obese = 18	*P*
Baseline	11/22 (50%)	12/18 (67%)	0.35
6 wk	1/21 (5%)	6/17 (35%)	0.03
6 mo	3/22 (14%)	6/17 (35%)	0.14
1 yr	6/22 (27%)	14/18 (79%)	0.004

Definition of abbreviation: SDB = sleep-disordered breathing.
P value is for comparison between percentages of obese versus nonobese groups.

Relationship of Recurrence of SDB to Systemic BP

In the comparison group, there was no significant change in systolic or diastolic BP over the course of the study. In children with SDB, a decline in diastolic BP was evident at 6 months after surgery (Figure 2). This significant trend was observed in children who had no recurrence and also in those who ultimately had recurrence at the 1-year evaluation. In the latter group, there was a significant increase in systolic BP compared with preoperative levels and compared with those who did not have recurrence. In a model that included age, race, BMI, and AHI at the end of the follow-up period, AHI was a significant predictor of systolic ($P = 0.03$) and diastolic ($P = 0.0004$) BP 1 year after adenotonsillectomy.

Evaluation for Recurrence of Hypertrophy of the Adenoids after Adenotonsillectomy

Subjects who had recurrence of SDB were invited to undergo a clinical evaluation and/or airway radiograph. In contrast to surgical removal of adenoidal tissue, the removal of the tonsils is complete and therefore regrowth of the tonsils does not occur. Thus, the objective of the evaluation was to assess for regrowth of the adenoids. Eleven subjects had an airway radiograph; two of these subjects had regrowth of the adenoids. In one case, the adenoids were nonobstructive and in another case the adenoids were obstructive. Nine subjects did not have evidence of regrowth of the adenoids. The remaining nine subjects who had recurrence of SDB did not receive an evaluation. The reasons were change in address or a refusal to pursue further evaluation because of the significant improvement in their AHI after surgery.

DISCUSSION

Several new observations with important implications for clinical practice and for understanding the pathogenesis of SDB in children emerged from this study. We report for the first time the longitudinal outcome of adenotonsillectomy in healthy children, the important influence of BMI gain velocity and African-American race on recurrence of SDB, and the longitudinal changes in BP associated with the recurrence of SDB.

TABLE 3. MULTIVARIABLE LOGISTIC REGRESSION

	OR (*95% CI*)	1 *df* χ^2	Two-tailed *P* Value	Area under ROC curve (C-statistic) without Variable
BMI, baseline				
Full model (5 term)				0.92
Male sex	6.0 (0.65–125)	2.4	0.1	0.90
African-American race	14 (1.5–280)	5.6	0.02	0.88
Age	1 (0.55–1.9)	0.006	0.9	0.92
BMI, baseline	1.4 (1.1–1.9)	7.2	0.007	0.87
BMI slope	6.2 (2.0–38)	12.3	<0.001	0.84
BMI, 1 yr				
Full model (5 term)				0.92
Male sex	6.4 (0.70–133)	2.5	0.1	0.89
African-American race	16 (1.7–317)	6.2	0.01	0.87
Age	1 (0.54–1.9)	0.004	0.9	0.91
BMI, 1 yr	1.4 (1.1–1.9)	6.8	0.009	0.87
BMI slope	4 (1.4–22)	7.5	0.006	0.86
Mean BMI				
Full model (5 term)				0.92
Male sex	6 (0.66–130)	2.6	0.1	0.90
African-American race	15 (1.6–299)	6	0.01	0.88
Age	1 (0.54–1.9)	0.2	0.7	0.91
Mean BMI	1.4 (1.1–1.9)	7.2	0.007	0.87
BMI slope	5.2 (1.7–30)	10	0.001	0.86

Definition of abbreviation: BMI = body mass index; CI = confidence interval; *df* = degree of freedom; OR = odds ratio; ROC = receiver operating characteristic.

Multivariable logistic regression using three different models. The table shows the area under ROC curve (C-statistic) for each full model and for models reduced by the removal of one variable at a time.

An important observation made in this study relates to the timing of the assessment of SDB after adenotonsillectomy. To date, most postadenotonsillectomy outcome studies have focused on the assessment of SDB 6 to 16 weeks after surgery (24–26). Resolution of SDB during this window of time was usually interpreted as a cure for the disorder. However, the high rate of recurrence of SDB that we observed 1 year after surgery in both obese and nonobese children indicates that SDB is a chronic condition. In fact, the absence of a significant correlation between the 6-week postoperative AHI and AHI measured at any earlier or later time speaks to the limited predictive value of the 6-week evaluation. Furthermore, large BP increases in children who had recurrence of SDB and the independent association of AHI with both 1-year systolic and diastolic BP point to the potential morbidity of unrecognized residual SDB after adenotonsillectomy. In view of our findings, it would be clinically prudent to extend the traditional 6-week follow-up, commonly used in clinical practice, to at least a 1-year follow-up.

In our study population, adenotonsillectomy was associated with partial to complete resolution of SDB in both obese and nonobese children. Although in obese children the 1-year AHI decreased significantly from that measured preoperatively, the number of obese children with an AHI greater than 3 increased from 67 to 79%. On one hand, these findings appear to indicate the beneficial effect of adenotonsillectomy in all children with SDB independent of BMI. On the other hand, they suggest the presence of a subset of children who are refractory to a long-term benefit, and in fact susceptible to progression of SDB despite adenotonsillectomy. Although children who were obese at baseline were more likely to be refractory to the benefit of adenotonsillectomy, there was an additional and independent risk of SDB reoccurrence due to the rate of BMI gain during the duration of the study. These results highlight the differential disease mechanisms between those due to obesity and those due to the rapid change in body composition associated with accelerated BMI gain.

Different obesity-related conditions and parameters, as distinct mediators of disease morbidity, have emerged from studies of pathways linking obesity to abnormal glucose homeostasis and cardiovascular diseases. Among these conditions is adiposity rebound, defined by the age after infancy at which BMI starts to rise and measured as BMI gain from birth to childhood. The role of BMI gain from infancy to childhood in obesity-related morbidity was highlighted by Bhargava and colleagues (27). In their

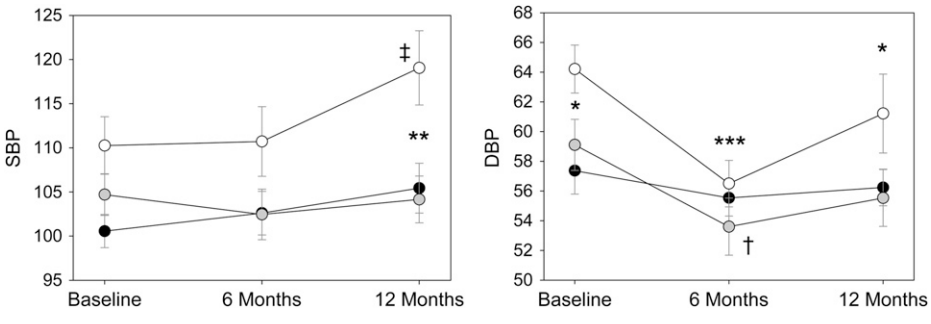

Figure 2. Trend of systolic blood pressure (SBP) and diastolic BP (DBP) from baseline to 6 months postadenotonsillectomy, then to 1 year postadenotonsillectomy in children who had no recurrence of sleep-disordered breathing (SDB) and those who had recurrence of SDB. Data from the comparison group are shown. For comparisons between the two SDB groups: $^{*}P < 0.05$, $^{**}P < 0.01$; for across time point, within-group comparisons: $^{\dagger}P = 0.02$ baseline versus 6 months, $^{\ddagger}P = 0.03$ baseline versus 1 year, $^{***}P = 0.003$ baseline versus 6 months. *Solid circles*, control group; *shaded circles*, AHI < 3 group; *open circles*, AHI > 3 group.

study of 1,492 young adults, they examined the relation of serial changes in childhood BMI to impaired glucose tolerance in young adulthood. Children, in whom impaired glucose tolerance or diabetes later developed, were characterized by a low BMI between birth and 2 years of age, a young age at adiposity rebound, and a sustained accelerated gain in BMI until adulthood. A similar association between rate of weight gain and the risk of cardiovascular disease in children and adults has been recently described (18, 19, 28).

Our study, together with those noted above, regarding the independent role of BMI gain in disease development, clearly support the concept of BMI gain trajectory as an independent risk factor for SDB, diabetes, and cardiovascular disease. The association of BMI gain with abnormal glucose homeostasis and markers of early atherosclerosis in children (15, 27) is similar to the trend we observed between BMI gain and risk for SDB after adenotonsillectomy. The similarity in these trends raises the important question of whether SDB is one link between a high rate of BMI gain during childhood and abnormal glucose homeostasis and cardiovascular disease in adulthood.

In all regression models examined in our study, being African American increased the risk of recurrence of SDB after adenotonsillectomy. This observation identifies the racial differences in conferring the risk of developing SDB in children.

A limitation of this study design is that it did not address the reproducibility of AHI in untreated children with SDB over a 1-year period. Because measuring the reproducibility of AHI over a period of 1 year in children with varying degrees of severity of SDB would require withholding therapy, and is not ethically acceptable, we included a healthy control group, which was followed for the same duration as children with SDB. Although the findings derived from the comparison group do not necessarily reflect the reproducibility of AHI in children with SDB, they nevertheless demonstrate the small variation of this index over a period of 1 year.

Conclusions

There is a high risk of recurrence of SDB in children 1 year after adenotonsillectomy that was associated with increasing BP. Gain velocity in BMI, being obese, and being African American increased the risk of recurrence of SDB 1 year after adenotonsillectomy. We advocate long-term follow-up of children with SDB, monitoring of BMI gain, and reevaluation of children who demonstrate rapid BMI gain, especially those who are African American.

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