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Secondary Analyses of the Childhood Adenotonsillectomy Trial
A Narrative Review

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IMPORTANCE Adenotonsillectomy, performed for approximately 500 000 children annually in the US alone, is the first line of treatment of pediatric obstructive sleep apnea (OSA). The Childhood Adenotonsillectomy Trial (CHAT), the first randomized clinical trial to test the efficacy of adenotonsillectomy, compared the management of pediatric nonsevere OSA by early adenotonsillectomy (eAT) vs watchful waiting with supportive care. Since the publication of the primary article in 2013, the CHAT study data set were made available via the National Sleep Research Resource, which allowed researchers to address a range of additional clinical questions relevant to the care of children with OSA. This review focuses on secondary analyses associated with the CHAT data set as grouped by the outcome of interest.

OBSERVATIONS The results of most secondary analyses suggest that children who underwent eAT experienced the greatest improvements in symptom burden, sleepiness, parent-reported behavior, and quality of life. Changes in other domains, such as cognition, cardiovascular physiology, and metabolic indicators, were modest and selective. The associations between most treatment outcomes and polysomnographic parameters were weak. Symptoms were poor predictors of OSA severity. The results from these secondary analyses benefitted from the rigor of multicenter design and centralized polysomnography interpretation in CHAT. However, the exclusion of younger preschool-aged children and children with primary snoring limited the generalizability of findings. In addition, because caregivers were not masked, some of the parent-reported outcomes may have been inflated.

CONCLUSIONS AND RELEVANCE The results of this narrative review suggest that CHAT provides a model for future OSA-related studies in children for design, conduct, and subsequent reuse of the study data set, and its findings have advanced our understanding of the pathophysiology and management of pediatric nonsevere OSA. Directions for future research include whether the findings from this landmark study are generalizable to younger children and children with primary snoring and severe OSA. Similar studies may help address practice variability associated with pediatric OSA and help identify children who are most likely to benefit from undergoing eAT.

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Supplemental content

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Obstructive sleep apnea (OSA) affects 5% of children and is associated with lower cognition,[1] problem behaviors,[2] impaired quality of life,[3] and cardiovascular disease risk.[4] The first line of management of childhood OSA is adenotonsillectomy (AT), which is followed by the resolution or improvement of the condition in most children.[5] Despite AT being the most common surgical procedure performed after administering general anesthesia in children younger than 15 years,[6] to our knowledge, there are few prospective studies of its efficacy because of the practical challenges associated with the design and conduct of randomized clinical trials of a widely accepted surgical procedure.[7]

The Childhood Adenotonsillectomy Trial (CHAT) was the first multicenter randomized clinical trial to evaluate the efficacy of AT for nonsevere OSA treatment. A total of 464 study participants aged 5 to 10 years with a diagnosis of OSA based on apnea hypopnea index (AHI) score of 2 to 30 or obstructive apnea index score of 1 to 20 were randomized into those who underwent early AT (eAT) within 4 weeks of enrollment or others who were followed with a strategy of watchful waiting with supportive care (WWSC). Exclusion criteria included recurrent tonsillitis, a *z* score based on a body mass index (BMI; calculated as weight in kilograms divided by height in meters squared) of 3 or more, and medication for attention deficit–hyperactivity disorder. All children underwent comprehensive postrandomization assessments at baseline and 7 months. These assessments included polysomnography, anthropometry, blood pressure measurements, neuropsychological testing, caregiver reports of children's behavior, symptom burden, and quality of life. The investigators hypothesized that the children who underwent eAT would have greater improvement in NEPSY attention/executive function scores compared with WWSC.

Subsequent to the primary articles,[7,8] the CHAT data set was made available on the National Sleep Research Resource (NSRR).[9,10]

Any investigator, not just those who participated in CHAT, could request access to the data set to examine additional research questions associated with pediatric OSA. The NSRR is an electronic library of data sets for hypothesis generation and discovery in sleep medicine. Aided by the NSRR, the CHAT was followed by approximately 30 publications of post hoc analyses ranging from cardiometabolic effects of OSA to prediction of OSA severity. The objectives of this study were to, (1) review the key findings from all post hoc analyses of CHAT data, (2) assess how these findings are associated with clinical management of nonsevere pediatric OSA, and (3) identify areas of future research.

Methods

From November 1, 2021, to December 31, 2021, we searched PubMed for secondary analyses associated with CHAT starting from the publication of the primary article[8] on June 20, 2013, to January 1, 2022. Search terms included *CHAT* and *Childhood Adenotonsillectomy Trial*.

Observations and Discussion

The search yielded 40 results, which were manually screened to include 27 original research reports of secondary analyses. Others included commentaries and duplicate publications. In this article, we reviewed the central findings from these articles as grouped by the following domains: (1) cognition (n = 1), (2) behavior (n = 2), (3) quality of life and symptomatology (n = 4), (4) growth (n = 2), (5) cardiovascular and metabolic effects (n = 8), and (6) risk factors for OSA (n = 10). These domains were chosen based on prior knowledge of the adverse effects of pediatric OSA, as well as the broad theme of each secondary analysis. Individual studies are summarized in the eTable in the Supplement.

Predictors of OSA Severity, Spontaneous Resolution, and Treatment Response

The CHAT demonstrated that AHI normalized in 79% of children in the eAT group compared with 46% of children in the WWSC group. Post hoc analyses of CHAT have focused on predicting OSA severity and identifying prognostic factors for treatment response.

Weinstock et al[11] showed that African American race and secondhand tobacco smoke exposure was associated with OSA severity after adjustment for prematurity, maternal education, and family income. Wang et al[12] showed that a greater percentage of single female–headed households and higher unemployment rates were associated with OSA severity when adjusted for obesity, asthma, prematurity, and maternal education. However, controlling for neighborhood-level factors mitigated the association between African American race and AHI, suggesting that socioeconomic disadvantage largely explains the higher severity of OSA among African American children.

Mitchell at al[13] showed that African American race and symptom burden are strongly associated with AHI, although they accounted for less than 3% of the variance in OSA severity. Isaiah et al[14] created a parsimonious prediction model for OSA severity derived from common OSA-specific symptom and quality of life questionnaires using variable selection methods. These included witnessing apneic events, perceived growth delay, mouth breathing, and obesity, which emphasized the need to focus on these symptoms during evaluation before AT. All study participants received a diagnosis of OSA, which limits the generalizability of each of these studies.

Paruthi et al[15] used capnography to predict OSA severity, cognitive outcomes, and behavioral outcomes. Capnography metrics were positively associated with AHI but not cognitive or behavioral outcomes.

Chervin et al[16] identified lower AHI and less central obesity as being associated with spontaneous resolution of OSA in the WWSC group. The only factors that were significantly associated with improvement of symptoms were baseline symptoms and snoring. Together, these findings support WWSC as a viable treatment option for children with mild OSA who have a low baseline symptom burden. Conversely, children with poor quality of life and high Pediatric Sleep Questionnaire scores at baseline should be considered for AT. Gourishetti et al[17] demonstrated that baseline severity of OSA was not associated with any of the response variables (eg, cognition, behavior, quality of life, and sleepiness) in the WWSC or the eAT group, supporting the need to identify a better predictor of treatment outcomes than the use of an AHI score of greater than 5 as a preoperative threshold in some guidelines.[18]

Rosen et al[19] demonstrated a strong positive association between baseline symptoms and parent-reported measures, including problem behaviors, as well as overall and disease-specific quality of life. The findings supported using symptom burden to identify children more likely to experience improvement in parent-reported outcomes. Hilmisson et al[20] used pulse oximetry to predict polysomnography-derived AHI scores. These data show promise for single sensor–based home sleep apnea testing in children.

In summary, results from CHAT-related studies confirmed previously observed associations between OSA and lower maternal education, urban settings, low education–level parental occupations, and low family income.[21,22] Although some predictors of OSA severity have been identified in secondary analyses, the factors associated with adverse outcomes in children with OSA and their response to treatment represent an important area for future research.

Cognition

Previous observational studies appeared to suggest that children with OSA have lower general intelligence, language, visuospatial, and memory skills compared with non-OSA controls.[5,23,24] Therefore, the primary outcome of the CHAT study was the postrandomization change in the attention and executive function score on the Developmental Neuropsychological Assessment (NEPSY A/E).[25] The NEPSY is a cognitive test with well-established psychometric properties and comprises 3 tasks (tower building, visual attention, and auditory attention) performed with the supervision of a psychometrist. The primary article showed that the study groups did not differ significantly in the NEPSY A/E at follow-up.[8] The average baseline cognition of children enrolled in CHAT was no different from normative data for the test, which contradicts previous studies. A possible explanation for the higher than anticipated cognition scores in CHAT may be associated with the fact that most children in this study had mild OSA.

While the original article did not demonstrate overall differences in cognition between the treatment groups, additional analy-

sis by Taylor et al[26] identified small and selective improvements in nonverbal, sequential, and quantitative reasoning in the eAT group compared with WWSC. However, scores did increase in both groups, suggesting a potential practice effect, which is the improvement observed over time attributed to increased familiarity with the task.

With these findings placed within the context of other randomized clinical trials,[27,28] there is little justification for performing AT to improve children's cognition and academic performance. The lack of association between polysomnographic parameters and baseline and follow-up cognitive scores suggests that clinicians should avoid using polysomnographic indices solely to identify children for AT. Further research is needed to better identify predictors of outcomes and the extent of improvement following surgery. Indeed, the Pediatric Adenotonsillectomy Trial for Snoring[29] addresses some of the gaps in knowledge, ie, the role of surgery in mild sleep disordered breathing and its selective association with response inhibition as measured by the Go-No-Go task, which is thought to be more sensitive to the effect of intermittent hypoxia on the brain. The benefits of eAT in terms of cognition in children with severe OSA and younger children remain unanswered with CHAT and warrant further investigation.

Caregiver-reported Behavior

Common problem behaviors in children with OSA include inattention and hyperactivity.[5] In the CHAT, children in the eAT group experienced larger improvements in behavior from baseline on parent-reported scales than children in the watchful waiting group. Teacher-reported behavior scales did not improve following adenotonsillectomy for the eAT. This finding may be explained in part by a substantial amount of missing teacher report data.

In secondary analyses of Child Behavior Checklist scores, Thomas et al[30] showed that children who underwent eAT had greater improvements in the domains of total, internalizing, and thought problems. Isaiah et al[31] showed that polysomnography parameters representing severity of obstruction, hypoxemia, sleep structure, and quality were not associated with parent-reported or teacher-reported behavior at baseline or follow-up in either group. Parent-reported symptoms of OSA are associated with worse Child Behavior Checklist scores, which are also accompanied by lower volumes of frontal lobe regions that are central to attention and response inhibition.[2] Some of the observed associations between symptoms and caregiver-reported children's behavior may be explained by the presence of shared items (ie, similar questions about sleep may be present in symptom and behavior questionnaires).

Hodges et al[32] investigated depressive symptoms in CHAT using the Children's Depression Inventory. Children with OSA self-reported higher levels of much above average depressive symptoms. At baseline, African American children self-reported higher levels of much above average depressive symptoms. Although depressive symptoms improved in both groups during follow-up, there were no significant postrandomization between-group differences in these scores.

In summary, the results from the CHAT data set are consistent with previously observed robust improvements in caregiver-reported behavior after AT and support offering the procedure routinely to children with OSA and adverse behavior reported by the parents.[5,33] However, a substantial limitation of these findings is that caregivers were not masked to the intervention, which can be associated with inflated reporting. Future studies may consider observational studies with propensity score matching to mitigate the potential reporting bias.

Symptom Burden and Quality of Life

A theme associated with the post hoc analysis of symptom and quality of life measures is their poor associations with OSA severity, as shown by Mitchell et al.[13] To explain the mechanistic associations between predictors and outcomes, a formal mediation analysis is useful. Most previous nonrandomized studies demonstrated significant gains in children's quality of life and sleepiness following eAT.[34] In CHAT, the eAT group experienced significantly greater improvement in symptom burden, sleepiness, and overall as well as disease-specific quality of life than the WWSC group.[8,15,35-37] In the WWSC arm in CHAT, despite almost half of the children having normalization of AHI scores at follow-up, the symptom burden remained high, with most children having a Pediatric Sleep Questionnaire–Sleep-Related Breathing Disorder scale score of greater than 0.33.[16]

Nocturnal enuresis, a common symptom in children with OSA, is explained by the potential association of OSA with arousal response, bladder pressure, or urinary hormone secretion.[38] In CHAT, the odds of nocturnal enuresis in the WWSC group were 2 times higher than the eAT group.[37] Thus, eAT may confer greater benefit for children with enuresis and OSA than WWSC. These results reinforce the need to inquire about bedwetting in children with OSA and potentially offer AT as a treatment option, although the long-term outcomes remain unclear.

Garetz et al[35] identified weak associations between OSA severity as measured by the AHI and improvements in symptoms and disease-specific quality of life. They also showed that the caregivers of African American children who underwent eAT reported less improvement than children from other racial and ethnic backgrounds, highlighting the need to investigate and address disparities in post-AT outcomes. Because of the poor association of AHI with quality of life outcomes, AHI should not be the sole factor used to determine candidacy for undergoing AT.

Liu et al[39] investigated the association of AT with thoracoabdominal asynchrony, an indirect marker of respiratory effort inversely associated with quality of life in children with symptomatic OSA.[40] Normalization of AHI scores following AT was followed by a significant decrease in thoracoabdominal asynchrony that was also associated with OSA symptom burden. Expansion of the airway following AT reduced the respiratory effort independently of AHI.

Paruthi et al[15] demonstrated a small association between a decrease in AHI scores at follow-up with improvement in sleepiness. Between 24.4% and 53% of children in CHAT had excessive sleepiness at baseline. Children who experienced normalization of AHI scores had a greater improvement in sleepiness than those with residual OSA. Bandyopadhyay and Slaven[36] showed that mouth breathing was the central symptom that contributed to poor quality of life in children in the CHAT cohort. The authors demonstrated that improvements in mouth breathing translated to less sleepiness and better behavior and quality of life. This association, independent of polysomnographic parameters, provides clinicians the ability to focus on specific clinical symptoms for maximizing treatment-related gains in qualitative domains, such as quality of life.

Isaiah et al[41] demonstrated a small but significant mediation effect of changes in OSA severity measured by the change in AHI scores

in the association between OSA treatment (eg, eAT vs WWSC) with symptoms and disease-specific quality of life. These findings suggest that a small proportion of the changes in symptoms and disease-specific quality of life could be explained by the greater reduction in AHI following eAT as opposed to WWSC.

These studies suggested that children with OSA experience substantially greater improvements in parent-reported symptoms of upper airway obstruction, sleepiness, and quality of life following eAT compared with WWSC. The magnitude of these benefits, along with their convergent validity associated with objective assessments based on mediation analysis, provide a clinician with robust information for parental counseling as part of shared decision-making. Future studies are necessary to identify predictors of improvement in quality of life and symptoms and whether similar benefits of eAT are observed in children with milder forms of sleep-disordered breathing.

Growth

Obstructive sleep apnea is often associated with poor growth[42,43] that is potentially associated with greater nocturnal work of breathing and abnormal growth hormone secretion.[44] Katz et al[45] showed that the eAT group experienced greater weight gain compared with the control group. Furthermore, 52% of children who had overweight at baseline developed obesity at follow-up in the eAT group compared with 21% in the WWSC group. Based on these results, the investigators discussed the importance of nutritional counseling and physical activity in children after AT, especially in children with overweight. Gourishetti et al[46] demonstrated that a significant proportion of post-AT weight gain in children with OSA is mediated by reduction of fragmentation of rapid eye movement sleep and a subsequent reduction in metabolic expenditure. However, a second analysis by Kirkham et al[47] found that there were similar rates of weight gain between the eAT and WWSC groups. The key difference between these studies is that the first study focused on the mechanistic aspects of weight gain in solely the children who gained weight following eAT. These findings, within the context of a randomized clinical trial, may help assuage concerns among clinicians and families who may be hesitant to proceed with AT for children with obesity or overweight.

Caregivers should also be counseled regarding realistic expectations concerning higher rates of residual OSA in children with obesity. Alternatives, such as continuous positive airway pressure and nutritional management, should also be discussed. Conversely, children with concerns for poor weight gain and/or failure to thrive are likely to experience normalization of their growth trajectory.

Cardiovascular Physiology and Metabolism

Untreated OSA is associated with elevated blood pressure, higher heart rate variability (HRV), and elevated levels of inflammatory markers, such as C-reactive protein,[5] although this association could also be confounded by comorbid obesity, which is associated with higher risk for OSA as well as elevated inflammatory markers.[48] Quante et al[49] evaluated the association of AT with cardiometabolic markers, including insulin, glucose, lipids, C-reactive protein, blood pressure, and heart rate. There was no association of treatment with postrandomization changes in any of the cardiometabolic markers. However, children who normalized their AHI scores, regardless of treatment arm, had significantly decreased heart rates. While this decrease in heart rate following treatment of OSA may not have immediate clinical significance, some studies have indicated that a meaningful decline in heart rate is beneficial in primary prevention of hypertension in children at risk.[50,51] The long-term clinical implications of these findings remain unclear, and further studies are necessary to establish the benefits of OSA treatment on children's cardiovascular health.

Although Baumert et al[52] identified a significant reduction in heart rate in the eAT group, pointing to potential favorable changes in sympathovagal balance in this group, it is unclear whether this is a clinically meaningful effect. Heart rate variability, a surrogate marker for cardiac autonomic activation, represents the variability in the interbeat interval of heart rate. Too high or low variability may be pathologic,[53] while children with OSA have lower HRV. Liu et al[54] demonstrated a greater reduction in monotonous increases or decreases in heart rate in the eAT group, suggesting its positive association with autonomic cardiovascular control.

Isaiah et al[55] analyzed typical time and frequency domain HRV parameters collected during polysomnography from the CHAT study. At baseline, HRV indices were similar to normative data. Children in the eAT group had a larger decrease in HRV parameters at follow-up, although this change was not associated with changes in AHI. Using spectral analysis, Martin-Montero et al[56] identified a distinct pattern in HRV (BW2) that was associated with sleep disruptions and the duration of apneas.

Sleep events are increasingly described in terms of macrostructural and microstructural characteristics. Macrostructure refers to the temporal order of sleep based on successive epochs of conventional length, while microstructure, derived from scoring of phasic events, provides dynamic characteristics in the evaluation of normal and pathological sleep processes.[57] While the adverse associations of OSA with sleep macrostructure have been extensively investigated, to our knowledge less is known about the association between upper airway obstruction and sleep microstructure. Changes in sleep microstructure represented by cyclical alternating pattern (CAP) that are derived from dynamic changes in electroencephalography waveform amplitude and frequency during non–rapid eye movement sleep captures sleep fragmentation beyond conventional sleep staging. Hartmann et al[58] identified a statistically significant association between CAP and worse behavior and lower quality of life at baseline in the subgroup of children with moderate OSA. Given its potential sensitivity for qualitative outcomes, such as behavior, baseline CAP could be a potential candidate as a biomarker for post-AT outcomes of OSA.

Hilmisson et al[59] studied sleep quality index (SQI) scores in CHAT that were derived using cardiopulmonary coupling to provide an assessment of sleep duration, stability, fragmentation, and pathology.[60] Compared with their counterparts with high SQI scores (>80), children with a BMI between 5th and 85th percentile with low SQI scores (<60) had a significantly higher average heart rate during sleep and insulin/glucose ratio. Children with a BMI higher than the 85th percentile with low SQI scores had higher C-reactive protein levels, average blood pressures, fasting insulin levels, insulin/glucose ratio, and triglyceride levels. These study results suggest the higher risk of poor sleep in children with obesity and align with previous studies.[61] Future studies need to confirm whether biomarkers, such as HRV and CAP, are associated with outcomes and whether subtle cardiac changes affect long-term cardiovascular morbidity.

Overall Effect

CHAT addresses an unmet need to understand the association between AT and pediatric OSA outcomes, especially given the challenges of designing a randomized clinical trial of a widely accepted surgical procedure. Despite enrollment constraints, multiple high-volume children's hospitals facilitated study completion. Strengths included a large and diverse sample, a randomized design, and relatively low levels of missing data. The study findings provided high levels of evidence supporting the use of AT for symptomatic children with OSA while supporting conservative management over 7 months in less symptomatic children. The weight gain observed after AT among children with overweight highlighted the need for initiating interventions to address optimal weight management. Multiple publications from CHAT also identified the limited ability of traditional polysomnographic and clinical variables for predicting AT responses, as well as testing of several polysomnographic metrics. The study also identified a higher AHI severity and poorer response to surgery among African American children who were deemed AT candidates, highlighting the need to address disparities, which may manifest as adverse environments in underserved neighborhoods. Limitations include the relatively short follow-up, the relatively urban recruitment sites, and the exclusion of younger or older children for whom the outcomes may be different. A concern regarding the exclusion of preschool-aged children has been addressed by 2 other randomized clinical trials. The Pre-school OSA Tonsillectomy Adenoidectomy (POSTA) study (ACTRN12611000021976).[27] and the Karolinska Adenotonsillectomy (KATE) study (NCT02315911)[28] showed that the findings from CHAT may be generalizable to younger children. The Pediatric Adenotonsillectomy Trial for Snoring (NCT02562040), designed by CHAT investigators to study a wider age range (3-13 years) in children with primary snoring and mild OSA (AHI score <3), will be completed in 2022 and will further address the role of AT in children with milder disease.

Conclusions

The results of this narrative review suggest that the effect of the CHAT is evident through the dozens of publications generated from the data set. CHAT substantially improved the understanding of clinicians on pediatric OSA outcomes. CHAT also provided a model for future OSA-related studies in children for design, conduct, and subsequent reuse of the data via a data commons. It is expected that the data set will continue to be a high-quality resource for investigators to address important questions in this domain.

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