Accepted Manuscript

Frequency of snoring, rather than apnea-hypopnea index, predicts both cognitive and behavioral problems in young children

Dale L. Smith, David Gozal, Scott J. Hunter, Leila Kheirandish-Gozal

PII: S1389-9457(17)30129-6

DOI: 10.1016/j.sleep.2017.02.028

Reference: SLEEP 3342

To appear in: *Sleep Medicine*

Received Date: 20 November 2016

Revised Date: 31 January 2017

Accepted Date: 1 February 2017

Please cite this article as: Smith DL, Gozal D, Hunter SJ, Kheirandish-Gozal L, Frequency of snoring, rather than apnea-hypopnea index, predicts both cognitive and behavioral problems in young children, *Sleep Medicine* (2017), doi: 10.1016/j.sleep.2017.02.028.

Frequency of snoring, rather than apnea-hypopnea index, predicts both cognitive and behavioral problems in young children

Dale L. Smith[a,d,*], David Gozal[b], Scott J. Hunter[b,c], Leila Kheirandish-Gozal[b]

[a]Department of Public Health Sciences, The University of Chicago, Chicago, IL, USA

[b]Department of Pediatrics, The University of Chicago, Chicago, IL, USA

[c]Department of Psychiatry and Behavioral Neuroscience, Pritzker School of Medicine, Biological Sciences Division, The University of Chicago, Chicago, IL, USA

[d]Department of Psychology, Olivet Nazarene University, Bourbonnais, IL, USA

***Corresponding author:** Department of Psychology, Olivet Nazarene University, Bourbonnais, IL, 60914, USA. Tel.: +1(815) 939-5142.

E-mail address: dsmith8@olivet.edu (Dale L. Smith)

Abstract

Objective: Primary snoring (PS) and obstructive sleep apnea (OSA) not only affect the quality of sleep in a large number of young children, but have also been repeatedly associated with a variety of behavioral and cognitive problems. However, little is known about the potentially differing relationships of behavioral and cognitive pathology within the sleep disordered breathing (SDB) spectrum.

Method: This study examined data from an enriched for snoring community sample of 631 children aged between 4 and 10 years. Multivariate mixed models were used to assess the relationship between both snoring and the apnea-hypopnea index (AHI). Numerous cognitive and behavioral variables were used, while adjusting for several important demographic variables. These were followed by univariate analyses of individual measures and sensitivity analyses.

Results: Results indicated that snoring status is a significant predictor of general behavioral (p=0.008) and cognitive (p=0.013) domains, even after adjusting for baseline covariates and AHI severity. More frequent snoring was associated with poorer outcomes independent of AHI. However, AHI did not emerge as a significant predictor of the overall cognitive functioning domain (p=0.377). Additionally, although AHI was a significant predictor of the general behavioral functioning domain (p=0.008), the significance pattern and nature of its relationship with individual behavioral measures were inconsistent in post-hoc analyses.

Conclusion: The findings of this study suggest that general behavioral and cognitive function may decline with greater snoring severity. Further, snoring should not simply be assumed to represent a lower severity level of SDB, but should be examined as a potential predictor of relevant outcomes.

Keywords:

Introduction

Sleep disordered breathing (SDB) is characterized by breathing abnormalities resulting from increased collapsibility of the upper airway, ultimately affecting the quality of sleep. Sleep disordered breathing can range from primary snoring (PS), indicating the presence of snoring, but absence of gas exchange abnormalities during sleep, to obstructive sleep apnea (OSA), the more severe condition whereby in addition to habitual snoring, gas exchange abnormalities and sleep fragmentation are present to a lesser or greater degree [1]. Prevalence estimates for SDB in children vary widely, and are often contingent on the method of assessment. A recent review of studies involving large cohorts suggested that 1.5-27.6% of children may suffer from habitual snoring [1], although median estimates worldwide are around 11-12% [2-4], which is a finding that is also corroborated by surveys in the US population [5]. These sources also estimate OSA prevalence of 1.2-5.7% [1,2,4].

Clinical definitions of OSA often vary, but overnight detection of the presence of apneas and hypopneas during polysomnographic analysis, which is reported as the apnea-hypopnea index (AHI), is generally considered the gold standard for OSA diagnosis and provides severity estimates of SDB [6]. Commonly cited risk factors for SDB include: obesity [7,8], race [8,9], prematurity [1,3], tobacco smoke exposure [10], and asthma [11,12]. Interestingly, it remains unclear whether gender differences exist in child SDB prevalence [13], which contrasts with the well-known higher SDB prevalence in males in the adult population [14].

Cognitive and behavioral problems are among the most prominent symptoms in children with SDB. The presence of behavioral functioning problems, often involving impulsivity, anxiety, aggression, hyperactivity, and deficits in emotional regulation,

alertness, or attention to tasks, occur more frequently among both children with PS and those with OSA [15-20]. Additionally, the specific association between attention deficit hyperactivity disorder (ADHD) and sleep problems has been the topic of numerous studies, which have resulted in conflicting conclusions in meta-analyses examining this association [21-23]. Cognitive functioning problems have also been frequently reported in children with SDB [24-28]. These deficits often involve measures of intelligence, executive functioning, problem-solving, language, and memory. However, demonstrations of cognitive impairments have often been less robust than those reported when assessing behavioral outcomes, with some studies failing to detect significant differences between children with and without SDB [29]. For example, the only randomized clinical trial to date that examined the effects of adenotonsillectomy (T&A) treatment for SDB found significant improvements in behavioral functioning after 7 months compared to children assigned to a watchful waiting treatment arm, but cognitive/executive-functioning changes were small and less consistent [30,31].

Most existing studies used fairly small samples to assess psychological functioning, and many either reported snoring or AHI as the SDB measure of interest, but did not examine both. Two recent analyses of cognitive [32] and behavioral [33] functioning in a large sample of school-aged children indicated that significant increases are detectable in the magnitude of behavioral problems at any level of SDB severity, and that reductions in cognitive functioning are dependent on the level of SDB severity. However, to ensure coherence with common clinical cut-offs these two studies combined snoring and AHI measures into a single four-level SDB factor. The amalgamation of SDB into categorical clusters precluded estimates of potentially different dose-response

relationships between snoring and AHI severity, and cognitive or behavioral outcomes. This is particularly relevant, considering that snoring may not simply reflect reduced severity of SDB, but may represent a unique and complex phenotype of SDB [34].

The current study extended previous finds by re-examining previously published data from the aforementioned large pediatric cohort [32,33]. However, rather than combining snoring and AHI into a single factor representing severity of SDB, both of these variables were examined as initially measured (ie, ordinal (snoring) and ratio (AHI) in scale) using multivariate mixed effects models that allow for omnibus tests of multiple cognitive and behavioral outcomes, despite some missing data in several individual outcome measures.

Participants and Methods

Participants

Between 2006 and 2014, 1097 children were recruited from the Louisville and Chicago areas. Children from Louisville were recruited through collaboration with public schools, and children from Chicago were recruited through community announcements and distribution of materials in the University of Chicago medical center. Participating children had not been previously identified as suffering from, or otherwise clinically referred for assessment of, sleep-related pathology. However, invitation for complete evaluation in this study purposefully oversampled for those children whose questionnaires revealed the presence of snoring. The enrichment procedures were conducted randomly, whereby a 3:1 snoring vs non-snoring approach was routinely applied to enable oversampling of habitually snoring children under the estimated

prevalence of habitual snoring at 10-12% of all children in this age bracket [5]. Children were aged between 4 and 10 years. Demographic characteristics of the sample are outlined in Table 1.

Although strength of the current multivariate analytical approach was the ability to accommodate missing outcome data, only participants with information on age, race, sex, asthma status, BMI, snoring status, and AHI were included in the analyses. Additionally, because a very small number of children who reported race other than Caucasian or African-American existed, due to power considerations, only children from these two racial groups were utilized for the current analysis. The resulting active sample retained for the present analysis was 631 children. This study was approved by University of Louisville (protocol #474.99), and the University of Chicago (protocol 09-115-B) Human Research Ethics Committees.

Measures

Behavioral assessments

The Conners' Parent Rating Scales-Revised (CPRS-R) [35] and Child Behavior Checklist (CBCL) [36] utilize parent ratings to determine the occurrence and severity of a variety of problematic behaviors in children. Three domains from the CPRS-R (Hyperactivity, Inattention, and Psychosomatic) and two domains from the CBCL (Internalizing and Externalizing) were utilized for the current study. Further information about these scales can be found in the online supplemental materials. Both the CBCL and CPRS-R have shown acceptable psychometric properties upon examination. Estimates of internal consistency are strong for all subscales of the CPRS-R (0.77-0.93) [35] and the CBCL (0.71-0.89) [37]. Since both scales were designed as screens for clinical use, a wealth of

research has examined, and generally supported, their use for detecting a variety of childhood conditions involving emotional or behavioral problems [38-40]. A recent meta-analysis has also suggested moderately strong-pooled sensitivity of 0.75 and 0.77 and specificity of 0.75 and 0.73 for the CPRS-R and CBCL, respectively, for detecting ADHD in children and adolescents [41].

Cognitive assessment

Both verbal and nonverbal scores on the Differential Ability Scale (DAS) [42] were used to assess intellectual functioning areas of the cognitive domain. More detailed information regarding cognitive assessment scores is included in online supplemental materials. Internal reliability estimates for the DAS are >0.70 for all subtests, and inter-rater reliability estimates are >0.90 [42]. Overall DAS performance is moderately-to-strongly associated with other measures of general intellectual functioning such as the Wechsler scale and Kaufman test [43]. Empirical evidence is more supportive of the clinical utility of overall cluster scores, rather than individual subscores for the DAS [44,45]. For this reason, only verbal and nonverbal cluster scores were utilized for this analysis.

Selected individual subtest scores from both the NEPSY and the NEPSY-II [46] were also used as part of the cognitive assessment to capture potential deficits in a variety of neurocognitive domains. The NEPSY is a neuropsychological assessment measure consisting of numerous cognitive tasks across six functional domains. Three were utilized in the present study: *Attention/Executive-Functioning, Language Ability,* and *Visuospatial Processing* domains. The *Attention/Executive-Functioning* tests chosen for this research were the *Visual Attention* and *Tower* subtests from the original NEPSY.

Psychometric properties of the NEPSY have been demonstrated to be strong. Internal consistency and split-half reliability estimates for the NEPSY subtests used here range from 0.79-0.91, and inter-rater reliability estimates are >0.97 [47,48]. Subtests have also been found to have moderate-to-large associations with relevant subtests of other established measures, such as Wechsler Intelligence tests and Delis-Kaplan Executive Functions System (D-KEFS) [48]. Assessments in clinical samples, such as children with traumatic brain injury, intellectual disability, autism, or disorders of functioning in cognitive-specific domains, have also supported the ability of the NEPSY to identify cognitive problems in clinical samples [48].

Procedure

All children were assessed overnight through standard nocturnal polysomnography (NPSG). Estimates for AHI were scored according to American Academy of Sleep Medicine guidelines by pediatric sleep experts, as described in previous research [32,33] and detailed in the online supplement for this report. Scorers were blind to cognitive and behavioral test results. During the morning, following NPSG assessment, children were asked to complete the cognitive tasks outlined above, and parents responded to standardized surveys concerning sleep habits and behavioral outcomes. Snoring status was reported by a parent as “never,” “rarely” (once per week), “occasionally” (twice per week), “frequently” (three times per week), and “almost always” (more than four times per week) as part of a validated and commonly used questionnaire [49]. Prior research examining parent-reported snoring status in relation to PSG analysis of snoring has demonstrated high sensitivity (0.66-0.94) and moderate to high specificity (0.20-0.73), depending on specific snoring cut-off values used for analyses [49,50].

Analytic strategy

All cognitive and behavioral measures were converted to z-scores to ensure equivalence of scale. Additionally, because behavioral measures were not normally distributed, a Box-Cox transformation [51] was utilized prior to computing standard scores for behavioral measures. This transformation was of the form:

$$y^{(\square)} - (y^{(\square)} - 1)/\square$$

in which $\square$ values ranged between –2.40 and 1.02 for the five behavioral measures. Additionally, because of strong positive skew and use of interaction terms in modeling, a log transformation was applied to AHI, which was then median centered.

The method of constructing this multivariate mixed model dataset required dummy coding for the dependent variables (behavioral and cognitive measures) and running the analysis by treating the dummy codes as random effects in the model. In essence, each dependent was allowed measure to have a different intercept, and these intercepts were treated as random effects. This created a two-level model, despite the lack of clustering (aside from the dependent measures) or longitudinal data. In the current models, nine cognitive outcome measures and five behavioral outcome measures were obtained from each individual. Although not utilized in the current analysis, multivariate mixed models can also include clustering, which allows for random intercepts and/or random slopes. In such an analysis, correlations between the dependent measures could be analyzed to determine to what extent unexplained correlations depend on the group or individual level.

Following separate omnibus multivariate tests for cognitive and behavioral measures, post-hoc univariate analyses for each measure were conducted to assess relationships between sleep pathology variables and individual cognitive or behavioral

measures. Covariates and/or interaction terms were included based on results of omnibus significance tests. Due to the inability for omnibus multivariate tests to sufficiently control the increase in Type I (familywise) error when conducting follow-up univariate tests [52], Rom's recent modification of Hochberg's step-up procedure [53] was used to correct for familywise error for all omnibus comparisons following likelihood ratio tests to compare multivariate models. Like Hochberg's step-up procedure [54], this approach controls Type I error levels by modifying the significance level criterion based on number of statistical tests, but has been shown to be slightly more powerful than Hochberg's or Bonferroni's corrections [53]. All analyses were completed using Supermix statistical software (Scientific Software International), and figures were created in Sigmaplot (Systat Software).

Results

The measures for cognition and behavior were significantly correlated (all *p*-values <0.01), supporting the possibility of underlying cognitive and behavioral constructs (see Tables 2 and 3; see online supplemental materials for behavioral and cognitive measure sample means). Supermix software output variance-covariance matrices closely approximated initial estimates. Initial screening indicated that none of these covariates moderated the relationship between sleep variables and behavior or cognition. Therefore, interaction terms were not included in the reported results. Snoring and AHI were significantly (but only moderately) related (r_s =0.24, p<0.01), as a high proportion of both low AHI children (AHI<1; 57.5%) and high AHI children (AHI>5; 88.3%) snored at least *frequently*.

Behavioral outcomes

When compared to an empty model, models including sex and asthma status fitted data significantly better (see Table 4). Females and children without asthma had better behavioral functioning overall, although age, race, and BMI status were not significant predictors of behavior. However, because of their important role in prior studies, the present study adjusted for all five of these demographic variables in analyses examining sleep variables.[a] Sensitivity analyses suggested that the pattern of significance for sleep variables was the same, regardless of their inclusion.

A model including AHI was a significantly better fit when compared to a model containing only demographic covariates (Δdeviance(5) = 15.55, $p<0.01$). The addition of snoring status also resulted in significantly greater fit relative to the model that included AHI (Δdeviance(20) = 38.55, $p<0.01$). However, the inclusion of AHI by snoring status interaction terms did not significantly improve model fit (Δdeviance(20) = 11.68, $p=0.93$). These results indicate that AHI and snoring status significantly predict overall behavioral pathology independently, and even when adjusting for the other in modeling. When inserting snoring status into the multivariate behavioral model first, the addition of AHI significantly improves model fit as well ($p<0.01$). Fig. 1 illustrates behavioral measure trends by snoring and AHI status.

Follow-up univariate analyses examining behavioral measures separately used the aforementioned modified Hochberg step-up approach for familywise error correction. Results indicated that snoring status categories *occasionally*, *frequently*, and *almost always* were associated with significantly greater behavioral functioning problems compared to *never* snoring across all five behavioral measures (see Table 5). Snoring

rarely was associated with significantly more behavior problems than *never* snoring only for psychosomatic problems. Varying the snoring reference category revealed that no significant differences existed between snoring severity/frequency levels among children who snored at least *rarely* in any behavioral measure.

Although AHI significantly predicted overall behavioral functioning in the multivariate analysis, AHI was not a significant predictor of psychosomatic, internalizing, or externalizing problems in follow-up univariate analyses. Surprisingly, higher levels of AHI were actually associated with significantly fewer behavior problems in hyperactivity ($B = –0.02$; $p<0.01$) and inattention ($B = –0.03$; $p<0.01$). Thus, greater levels of parentally reported behavioral problems existed across all measures among children according to snoring status, but higher AHI was associated with fewer problems in hyperactivity and inattention.

Cognitive outcomes

When compared to an empty model, models including age, sex, race, and asthma status fitted data significantly better (see Table 6). Older children, females, white children, and children without asthma generally performed better on cognitive tasks. Although BMI was not a significant predictor of cognition, it was included in subsequent models using sleep variables to predict cognition, due to its prominence in prior research.

Adjusting for the (baseline) covariates noted above, adding AHI did not result in significantly better model fit in the multivariate model predicting cognitive functioning (□deviance(9) = 9.68, p=0.38). However, adding snoring status did result in significantly better model fit relative to a model with baseline covariates and AHI (□deviance(36) = 57.43, p=0.01). The addition of AHI by snoring status interaction terms also did not

result in greater model fit (□deviance(36) = 36.96, p=0.42). These findings suggest that snoring status, but not AHI, is a significant predictor of overall cognition, even when adjusting for age, sex, BMI, race, asthma status, and AHI. However, none of these variables moderate the relationship between snoring and cognition. Fig. 2 illustrates the general trend toward reduction in overall cognition at higher levels of snoring severity, although some heterogeneity exists across individual cognitive measures.

Follow-up univariate analyses examining individual cognitive measures separately using Rom's modified Hochberg step-up procedure were performed as outlined above. Since the study was interested in the ability of snoring status to predict cognitive outcomes in the presence of, and adjusting for, AHI, AHI was included as a covariate in all models, despite lack of significance in omnibus multivariate analyses. The same baseline covariates noted above in the omnibus model were also adjusted for in follow-up univariate analyses. Results suggested that only NEPSY Comprehension of Instructions was consistently lower among snoring children relative to non-snorers, although this effect existed for *occasionally*, *frequently*, and *almost always* snorers, but not those who snored only *rarely* (see Fig. 3). Additionally, varying the snoring reference category revealed that differences in Comprehension of Instructions did not exist between snoring severity levels for children who snored at least *rarely*.

Sensitivity analyses

Several sensitivity analyses were conducted for both cognitive and behavioral outcomes beyond those discussed above. The first involved conducting standard multivariate multiple regression analysis, which required list-wise deletion of individuals missing any cognitive or behavioral outcome. This resulted in loss of 47 participants from analyses.

However, the results aligned very closely to those obtained in the mixed model, as reported above. Among cognitive outcomes, only snoring status was a consistently significant predictor, and in univariate analyses this effect was again primarily in regards to NEPSY Comprehension of Instructions. Among behavioral outcomes, the same pattern of results found above was obtained in this analysis as well; *occasionally* or more frequent snoring was significantly related to more behavioral pathology on all measures, and AHI was negatively associated with parent-rated inattention and hyperactivity.

The present study also examined snoring as a dichotomous variable, initially grouping all children who snore at any frequency and comparing them to children who do not snore. The cutoff was then varied to reflect different severity levels of snoring (eg, *occasionally* and greater snoring severity compared to *never* or *rarely*). As might be expected from examining Fig.1 and Fig. 3, snoring comparisons were significant when comparing *never* snorers to any *ever snoring* group, or when grouping *never* and *rarely* snoring and comparing them to those with more frequent snoring (at least *occasional* snoring). However, higher cutoffs, such as including *occasional* snorers in the low snoring severity group compared to *frequently* and *almost always* snorers, resulted in inconsistent significance patterns when comparing groups, as this comparison was significant only for psychosomatic and internalizing problems following adjustment for multiple comparisons.

Finally, AHI was examined as a categorical variable using commonly utilized AHI cutoffs of 1 and 5/hour total sleep time (TST). Group 1 consisted of children with AHI <1/hour TST, and represented children who would not be categorized as suffering from OSA. Group 2 consisted of children with AHI between 1 and 5/hour TST, which

represented children with mild OSA. Group 3 consisted of children with AHI >5/hour TST, representing moderate to severe OSA. This conceptualization was similar to previously published work [32,33], but allowed for an examination of an AHI variable isolated from snoring status, as well as the potential effects of AHI when adjusting for snoring status. Results aligned with the findings noted above; when adjusting for baseline covariates and snoring status AHI level was not a significant predictor of overall cognitive functioning (p=0.55), but was a significant predictor of behavioral functioning (p=0.04). However, as identified above, higher AHI levels were generally associated with fewer behavioral problems.

Discussion

The current study findings support and expand upon previous research that has generally illustrated a relationship between SDB and cognitive and behavioral outcomes. The significance of snoring status as a predictor of behavioral outcomes, even when adjusting for AHI, is a particularly salient and clinically relevant finding resulting from the present analyses. Across all behavioral measures, which spanned numerous clinically relevant domains using empirically validated measures, children who snored frequently were more impaired than non-snoring children. Sensitivity analyses supported the robustness of these findings to differing characterizations of sleep pathology and snoring status.

The lack of significant AHI effects may initially appear to contradict recent findings [32,33], which suggested that higher severity levels of SDB were associated with poorer cognitive outcomes, while the increase in behavioral pathology was generally prominent among all snorers with a leveling-off of behavioral problems at higher levels

of SDB severity. However, it should be noted that the conceptualization of the sleep pathology variables differed in those analyses, as snoring and AHI were combined to represent established clinical categories. Additionally, the reduction in behavioral problems with increased AHI is not without precedent. Indeed, prior research has demonstrated reductions in numerous behavioral domains with increasing AHI [55,56]. The current analysis expands on these findings by separately examining snoring and AHI, and indicates that behavioral pathology increases with frequency of snoring up to occasional snoring, but does not increase based on AHI severity. It may, in fact, slightly decrease for some measures with increasing AHI.

These findings suggest that snoring status should be carefully considered when studying any effects of SDB on cognition or behavior. Sleep pathology groupings that primarily utilize AHI may be effective and sensitive in relating sleep pathology to outcomes, and may be necessary in small-sample studies due to power considerations. However, this large cohort analysis indicates that snoring status may occasionally be a more effective predictor, particularly of behavioral outcomes, and those children who snore *occasionally* or more (at least 2 nights per week) are at particular risk, regardless of AHI measurements. Further, the relationship between snoring and AHI, although significant, was not particularly strong ($r_s = 0.24$), such that ignoring snoring status or assuming it is adequately captured through AHI measurements could neglect potentially interesting and informative findings. Indeed, a recent meta-analysis that classified severity exclusively via AHI found no severity-related differences in executive function in children [57].

The importance of snoring beyond what may be obtained through AHI has been previously suggested, but the mechanisms that may underlie any potential causal effect of snoring on cognitive or behavioral outcomes are unclear. Current theories on the mechanisms through which SDB affects psychologic outcomes generally involve deleterious effects of hypoxic insults and resulting stress or inflammation in the brain or repeated sleep disruption through arousals [15,58,59]. However, since neither of these features is consistently found among PS children [34], mechanisms through which snoring possibly affects behavior or cognition remain essentially unknown. Some authors have suggested that arousals and consequent sleep disruption may underlie this association, but that current guidelines and criteria for scoring arousals and attendant sleep disruption may not be sufficiently sensitive to detect sleep fragmentation in children with PS [60]. This could involve slight changes in electroencephalographic (EEG) signals that are not scored as arousals [61], or reflect sub-cortical activations without surface EEG arousals [62]. Further research is needed to determine whether these or other factors may mediate the currently identified relationships between snoring and cognitive and behavioral functioning. It should also be pointed out that the oversampling strategies to enhance the proportion of habitually snoring children may have potentially created some degree of bias, even if uncertainty exists as to the nature and impact of such putative assumption.

Future randomized clinical trials involving SDB intervention, such as T&A, and longitudinal examination of cognitive and behavioral outcomes, as they relate to changes in both PS and AHI, may prove particularly informative in better understanding this relationship. The only existing randomized clinical trial demonstrated significant

improvement in behavior, but only some degree of improvement in a subset of cognitive domains after seven months [30,31]. Whether significant changes in cognitive functioning should be expected after such a short delay following treatment, or whether permanent deficits may occur as a consequence of extended periods without restful sleep and gas exchange abnormalities during formative years, remains to be fully resolved. Numerous interventional studies that did not include controls have reported improvements in various behavioral and cognitive outcomes following T&A [63,64]. One recent meta-analysis has suggested that T&A may only result in improvement of cognitive functioning in pre-school-aged children [65], though not all longitudinal studies have identified a relationship between improvement in AHI and cognitive or behavioral outcomes in this age group [66]. This may suggest permanent effects of early SDB, or the presence of an SDB-cognitive phenotype.

Although a substantial proportion of childhood cases of SDB will naturally remit prior to adolescence [67], opinions differ on the appropriate approach and urgency of SDB treatment, given the potential risk for adverse medical and psychological outcomes if SDB is left untreated [68]. Indeed, as illustrated in the current analysis, various forms of behavioral and cognitive problems that may affect learning and school functioning often accompany both OSA and PS. A recent meta-analysis examining the potential impact of SDB on academic performance in children concluded that SDB was associated with poorer educational outcomes across multiple domains, although results concerning dose-response relationships were inconclusive [69]. The authors cited differing definitions and measures of SDB across studies as a potential cause for the lack of a graded impact of SDB severity. The results of the current analysis support this assertion

by demonstrating the importance of how SDB is characterized. Any relevant reduction in academic performance across multiple areas could potentially reflect the results of behavioral problems, such as inattention or impulsivity, or alternatively reflect a true reduction in cognitive functioning. Researchers have suggested that behavioral problems may mediate the relationship between sleep pathology and cognitive functioning or school performance [26]. Future research should further examine this potentially dynamic and informative set of relationships that may contribute to lower academic achievement in this population.

In addition to highlighting the importance of snoring status, this analysis also illustrated the unique advantages that are inherent to the use of a mixed model framework to accommodate multivariate tests, despite missing outcome data for some participants. In assessing multiple cognitive or behavioral outcomes, or using similar applications in which outcome measures are correlated and an underlying construct or linear combinations of outcomes are of interest, this may be particularly useful. This statistical method allows for the application of multivariate analyses, and thus permits a potentially more powerful omnibus test and examination of linear combinations of interest, without having to resort to list-wise deletion or use of multiple imputation methods. The utility of this method is illustrated here in the significance of snoring status as a predictor of overall cognition in multivariate results, as a general reduction in cognition existed with greater intensity of snoring, although individual univariate analyses with familywise error correction lacked sufficient power to detect this reduction. Power considerations in the selection of SDB measurements for analysis should also typically be acknowledged in

study planning, though sensitivity analyses here demonstrated the robustness of the results to different characterizations of SDB.

Several limitations should be noted in the present study. The most salient may be the inherent difficulty in drawing causal conclusions when dealing with observational data. Despite the wealth of research linking sleep pathology with cognitive and behavioral outcomes, much of this research, including the current analysis, has not adequately manipulated the underlying SDB to assess changes in measured outcomes. Although a recent clinical trial has supported the potential causal effects of SDB on behavioral outcomes [31], questions remain concerning the appropriate age of such interventions, and when deleterious effects of sleep pathology may begin or peak. Additionally, although the current analysis adjusted for variables such as race, age, sex, and BMI, other variables that were not measured, such as socioeconomic status, likely account for some variability in both behavioral and cognitive measures, and could confound these relationships.

Another potential limitation of the current analysis involves use of parent reports for both behavioral outcomes and snoring status. It is possible that parents who are aware of a possible link between SDB and behavioral problems could provide biased estimates of either measure. However, prior research using community samples has suggested strong associations between parent-reported and objectively measured snoring [49] and shown that parents are generally unaware of an association between SDB and psychiatric outcomes [70]. Thus, the potential for such bias here is likely low. Additionally, the use of community-based sampling reduces the likelihood of referral bias as an explanation for the association between SDB and reported outcomes.

Conclusions

The present analysis represents a unique multivariate approach to examining the potential effects of SDB on behavior and cognition. The findings indicate that snoring status is an effective predictor of a general problem behavior domain, which included behavioral outcomes involving parent-rated hyperactivity, inattention, psychosomatic problems, internalizing problems, and externalizing problems, even after adjusting for AHI and other variables of interest. Snoring was also a significant predictor of the overall cognitive functioning domain, though follow-up univariate analyses were significant only for the NEPSY Comprehension of Instructions task. In contrast, the polysomnographically-derived AHI was often non-significant as a predictor of cognition and behavior, and was negatively related to behavior problems in some measures. This emphasizes the importance of examining and including snoring status in assessments of potential cognitive and behavioral outcomes of pediatric SDB.

Footnote

a. *High BMI* was also examined as a categorical variable, using a cut-off BMI Z-score of 1.64. This variable was also non-significant as a predictor of all cognitive measures and all but one behavioral measure when adjusting for age, sex, race, and asthma status. Since characterizing BMI in this manner did not alter significance pattern of results for any existing analyses, results when using continuous BMI Z-scores were reported here.

Conflict of Interest: The authors have no conflict of interest to declare.

Funding Sources: This work was supported by grants from the National Institutes of Health R01-HL130984 to LKG and R01-HL65270 to DG.

References

1. Marcus CL, Brooks LJ, Draper KA, et al. American Academy of Pediatrics. Diagnosis and management of childhood obstructive sleep apnea syndrome. Pediatrics 2012; 130(3): e714-55.

2. Bonuck KA, Chervin RD, Cole TJ, Emond A, Henderson J, Xu L, et al. Prevalence and persistence of sleep disordered breathing symptoms in young children: a 6-year population-based cohort study. Sleep 2011; 34(7): 875-84.

3. Montgomery-Downs HE, Gozal D. Sleep habits and risk factors for sleep-disordered breathing in infants and young toddlers in Louisville, Kentucky. Sleep Med 2006; 7(3): 211-9.

4.Bixler EO, Vgontzas AN, Lin HM, Liao D, Calhoun S, Vela-Bueno A, et al. Sleep disordered breathing in children in a general population sample: prevalence and risk factors. Sleep 2009; 32(6):731-6.

5. O'Brien LM, Holbrook CR, Mervis CB, Klaus CJ, Bruner JL, Raffield TJ, et al. Sleep and neurobehavioral characteristics of 5- to 7-year-old children with parentally reported symptoms of attention-deficit/hyperactivity disorder. Pediatrics 2003;111(3): 554-63.

6. Rapoport DM. POINT: Is the Apnea-Hypopnea Index the Best Way to Quantify the Severity of Sleep-Disordered Breathing? Yes. Chest 2016; *149*(1):14-16.

7. Spruyt K, Gozal D. A mediation model linking body weight, cognition, and sleep-disordered breathing. Am J Respir Crit Care Med 2012; 185(2):199-205.

8. Redline S, Tishler PV, Schluchter M, Aylor J, Clark K, Graham G. Risk factors for sleep-disordered breathing in children: associations with obesity, race, and respiratory problems. Am J Respir Crit Care Med 1999; 159(5): 1527-32.

9. Dudley KA, Patel SR. Disparities and genetic risk factors in obstructive sleep apnea. Sleep Med 2016; 18: 96-102.

10. Montgomery-Downs HE, Gozal D. Snore-associated sleep fragmentation in infancy: mental development effects and contribution of secondhand cigarette smoke exposure. Pediatrics 2006; *117*(3): e496-e502.

11. Goldstein NA, Aronin C, Kantrowitz B, Hershcopf R, Fishkin S, Lee H, et al. The prevalence of sleep-disordered breathing in children with asthma and its behavioral effects. Pediatr Pulm 2015; 50(11): 1128-36.

12. Teodorescu M, Barnet JH, Hagen EW, Palta M, Young TB, Peppard PE. Association between asthma and risk of developing obstructive sleep apnea. JAMA 2015; *313*(2): 156-64.

13. Lumeng JC, Chervin RD. Epidemiology of pediatric obstructive sleep apnea. Proc Amer Thoracic Soc 2008; 5(2): 242-52.

14. Guilleminault C, Dement WC. Sleep apnea syndromes and related disorders. In: Williams RL, Katacan I, editors. Sleep Disorders: Diagnosis and Treatment. New York: Wiley; 1978.

15. Beebe W. Neurobehavioral morbidity associated with disordered breathing during sleep in children: a comprehensive review. Sleep 2006; 29(9): 1115.

16. Urschitz MS, Eitner S, Guenther A, Eggebrecht E, Wolff J, Urschitz-Duprat PM, et al. Habitual snoring, intermittent hypoxia, and impaired behavior in primary school children. Pediatrics 2004; 114: 1041-8.

17. Bonuck K, Freeman K, Chervin RD, Xu L. Sleep-disordered breathing in a population-based cohort: behavioral outcomes at 4 and 7 years. Pediatrics 2012; 129(4): e857-65.

18. Brien LM, Lucas NH, Felt BT, Hoban TF, Ruzicka DL, Jordan R, et al. Aggressive behavior, bullying, snoring, and sleepiness in schoolchildren. Sleep Med 2011; 12(7): 652-8.

19. O'Brien LM, Mervis CB, Holbrook CR, Bruner JL, Klaus CJ, Rutherford J, et al. Neurobehavioral implications of habitual snoring in children. Pediatrics 2004; 114: 44-9.

20. O'Brien LM, Mervis CB, Holbrook CR, Bruner JL, Smith NH, McNally N, et al. Neurobehavioral correlates of sleep-disordered breathing in children. J Sleep Res 2004; 13:165-72.

21. Sadeh A, Pergamin L, Bar-Haim Y. Sleep in children with attention-deficit hyperactivity disorder: a meta-analysis of polysomnographicnographic studies. Sleep Med Rev 2006; 10(6):381-98.

22. Cortese S, Faraone SV, Konofal E, Lecendreux M. Sleep in children with attention-deficit/hyperactivity disorder: meta-analysis of subjective and objective studies. J Am Acad Child Psy 2009; 48(9): 894-908.

23. Sedky K, Bennett DS, Carvalho KS. Attention deficit hyperactivity disorder and sleep disordered breathing in pediatric populations: a meta-analysis. Sleep Med Rev 2014; 18(4): 349-56.

24. Kheirandish L, Gozal D. Neurocognitive dysfunction in children with sleep disorders. Developmental Sci 2006; *9*(4): 388-99.

25. Kheirandish-Gozal L, De Jong MR, Spruyt K, Chamuleau SA, Gozal D. Obstructive sleep apnoea is associated with impaired pictorial memory task acquisition and retention in children. Eur Respir J 2010; 36(1): 164-9.

26. Biggs SN, Nixon GM, Horne RS. The conundrum of primary snoring in children: what are we missing in regards to cognitive and behavioural morbidity? Sleep Med Rev 2014; 18(6):463-75.

27. Brockmann PE, Urschitz MS, Schlaud M, Poets CF. Primary snoring in school children: prevalence and neurocognitive impairments. Sleep Breath 2012; 16(1): 23-9.

28. Spruyt K, Capdevila OS, Kheirandish-Gozal L, Gozal D. Inefficient or insufficient encoding as potential primary deficit in neurodevelopmental performance among children with OSA. Dev Neuropsychol 2009; 34(5): 601-14.

29. Hagström K, Saarenpää-Heikkilä O, Himanen SL, Lapinlampi AM, Ni-eminen P. Behavioral problems and neurocognitive functioning in snoring school-aged children. Psychol Cogn Sci Open J 2015; 1(2): 46-53.

30. Marcus CL, Moore RH, Rosen CL, Giordani B, Garetz SL, Taylor HG, et al. A randomized trial of adenotonsillectomy for childhood sleep apnea. NEJM 2013; 368(25): 2366-76.

31. Taylor HG, Bowen SR, Beebe DW, Hodges E, Amin R, Arens R, et al. Cognitive Effects of Adenotonsillectomy for Obstructive Sleep Apnea. Pediatrics 2016; 138(2): e20154458. doi: 10.1542/peds.2015-4458.

32. Hunter SJ, Gozal D, Smith DL, Philby MF, Kaylegian J, Kheirandish-Gozal L. Effect of Sleep-Disordered Breathing Severity on Cognitive Performance Measures in a Large Community Cohort of Young School-Aged Children. Am. J Respir Crit Care Med 2016; 194.(6): 739-47. DOI: http://dx.doi.org/10.1164/rccm.201510-2099OC

33. Smith DL, Gozal D, Hunter SJ, Philby MF, Kaylegian J, Kheirandish-Gozal L. The impact of sleep-disordered breathing severity on behavior among elementary school-aged children. Eur Respir J 2016; ERJ-00808. DOI: 10.1183/13993003.00808-2016

34. Biggs SN, Nixon GM, Horne RSC. The conundrum of primary snoring: What are we missing in regards to cognitive and behavioural morbidity? Sleep Med Rev 2014;18(6): 463-75.

35. Conners, CK. Conners' Rating Scales-Revised. North Tonawanda, NY: Multi-Health Systems; 1997.

36. Achenbach TM. Manual for the Child Behavior Checklist and 1991 profile. Burlington, VT: University Associates in Psychiatry; 1991.

37. Nakamura BJ, Ebesutani C, Bernstein A, Chorpita BF. A psychometric analysis of the child behavior checklist DSM-oriented scales. J Psychopathol Behav 2009; *31*(3):178-89.

38. Havdahl KA, von Tetzchner S, Huerta M, Lord C, Bishop SL. Utility of the Child Behavior Checklist as a Screener for Autism Spectrum Disorder. Autism Res 2015;9(1): 33-42.

39. Masi G, Muratori P, Manfredi A, Pisano S, Milone A. Child behaviour checklist emotional dysregulation profiles in youth with disruptive behaviour disorders: clinical correlates and treatment implications. Psychiat Res 2015; 225(1):191-6.

40. Zappitelli MC, Pereira ML, Bordin IA. Child Behavior Checklist-Mania Scale as a Screening Tool to Identify Children at Risk for Bipolar Disorder. J Child Adol Psychop 2015; 25(5): 448-9.

41. Chang LY, Wang MY, Tsai PS. Diagnostic accuracy of rating scales for Attention-Deficit/Hyperactivity Disorder: A Meta-analysis. Pediatrics 2016;137:1-13.

42. Elliott CD. Differential ability scales: handbook. San Antonio: The Psychological Corporation; 1990.

43. Elliott CD. The nature and structure of children's abilities: Evidence from the Differential Ability Scales. J Psychoeduc Assess 1990; 8:376-90.

44. Youngstrom EA, Kogos JL, Glutting JJ. Incremental efficacy of Differential Ability Scales factor scores in predicting individual achievement criteria. School Psychol Quart 1999; 14(1): 26.

45. Kahana SY, Youngstrom EA, Glutting JJ. Factor and Subtest Discrepancies on the Differential Ability Scales Examining Prevalence and Validity in Predicting Academic Achievement. Assessment 2002; 9(1):82-93.

46. Korkman M, Kirk U, Kemp S. NEPSY: a developmental neuropsychological assessment manual. San Antonio TX: The Psychological Corporation; 1998.

47. Ahmad SA, Warriner EM. Review of the NEPSY: A developmental neuropsychological assessment. Clin Neuropsychol 2001; 15(2): 240-9.

48. Brooks BL, Sherman EM, Strauss E. NEPSY-II: A developmental neuropsychological assessment. Child Neuropsychol 2009; 16(1): 80-101.

49. Spruyt K, Gozal D. Screening of pediatric sleep-disordered breathing: a proposed unbiased discriminative set of questions using clinical severity scales. Chest 2012; 142(6): 1508-15.

50. Montgomery-Downs HE, O'Brien LM, Holbrook CR, Gozal D. Snoring and sleep-disordered breathing in young children: Subjective and objective correlates. Sleep 2004; 27(1):87-94.

51. Box GEP, Cox DR. An analysis of transformations, J Roy Stat Soc Ser B Met 1964; 26: 211-52.

52. Bird KD, Hadzi-Pavlovic D. Controlling the maximum familywise Type I error rate in analyses of multivariate experiments. Psychol Methods 2014;19(2): 265-80.

53. Rom DM. An improved Hochberg procedure for multiple tests of significance. Brit J Math Stat Psy 2013; 66(1):189-96.

54. Hochberg Y. A sharper Bonferroni procedure for multiple tests of significance. Biometrika 1988;75(4):800-2.

55. Bourke RS, Anderson V, Yang JS, Jackman AR, Killedar A, Nixon GM, et al. Neurobehavioral function is impaired in children with all severities of sleep disordered breathing. Sleep Med 2011;12:222e9.

56. Brockmann PE, Urschitz MS, Schlaud M, Poets CF. Primary snoring in school children: prevalence and neurocognitive impairments. Sleep Breath 2012;16:23e9.

57. Mietchen JJ, Bennett DP, Huff T, Hedges DW, Gale SD. Executive function in pediatric sleep-disordered breathing: A meta-analysis. J Int Neuropsyc Soc 2016; 22:1-12.

58. Blunden SL, Beebe DW. The contribution of intermittent hypoxia, sleep debt and sleep disruption to daytime performance deficits in children: consideration of respiratory and non-respiratory sleep disorders. Sleep Med Rev 2006;10:109e18.

59. Gozal D, Kheirandish-Gozal L. Cardiovascular morbidity in obstructive sleep apnea: oxidative stress, inflammation, and much more. Am J Respir Crit Care Med 2008; 177: 369e75.

60. Jackman AR, Biggs SN, Walter LM, Embuldeniya US, Davey MJ, Nixon GM, et al. Sleep-disordered breathing in preschool children is associated with behavioral, but not cognitive, impairments. Sleep Med 2012;13:621e31.

61. Bandla HP, Gozal D. Dynamic changes in EEG spectra during obstructive apnea in children. Pediatr Pulmonol 2000;29:359e65.

62. Guilleminault C, Winkle R, Korobkin R, Simmons B. Children and nocturnal snoring: evaluation of the effects of sleep related respiratory resistive load and daytime functioning. Eur J Pediatr 1982;139:165-71.

63. Friedman BC, Hendeles-Amitai A, Kozminsky E, Leiberman A, Friger M, Tarasiuk A, et al. Adenotonsillectomy improves neurocognitive function in children with obstructive sleep apnea syndrome. Sleep 2003;26:999-1005.

64. Giordani B, Hodges EK, Guire KE, Ruzicka DL, Dillon JE, Weatherly RA, et al. Changes in neuropsychological and behavioral functioning in children with and without obstructive sleep apnea following Tonsillectomy. J Int Neuropsych Soc 2012;18(02): 212-22.

65. Song SA, Tolisano AM, Cable BB, Camacho M. Neurocognitive outcomes after pediatric adenotonsillectomy for obstructive sleep apnea: A systematic review and meta-analysis. Int J Pediatr Otorhi 2016; 83:205-10.

66. Biggs SN, Walter LM, Jackman AR, Nisbet LC, Weichard AJ, Hollis SL, et al. Long-term cognitive and behavioral outcomes following resolution of sleep disordered breathing in preschool children. Plos One 2015; 10(9): p.e0139142.

67. Bixler EO, Fernandez-Mendoza J, Liao D, Calhoun S, Rodriguez-Colon SM, Gaines J, et al. Natural history of sleep disordered breathing in prepubertal children transitioning to adolescence. Eur Respir J 2016; 47(5): 1402-9.

68. Campos-Rodriguez F, Martínez-García MA. Searching for the happy medium in the therapeutic approach to childhood sleep disordered breathing. Eur Respir J 2016; 47(5): 1310-12.

69. Galland B, Spruyt K, Dawes P, McDowall PS, Elder D, Schaughency E. Sleep disordered breathing and academic performance: A meta-analysis. Pediatrics 2015; 136(4): e934-46.

70. Strocker AM, Shapiro NL. Parental understanding and attitudes of pediatric obstructive sleep apnea and adenotonsillectomy. Int J Pediatr Otorhinolaryngol 2007; 71: 1709–15.

Tables

Table 1. Sample demographic characteristics (n=1055[a])

Characteristic	***M (SD) or n (%)*[a]**
Age	6.94 (1.30)
Sex (male %)	608 (55.42%)
Race (black %)[b]	420 (38.25%)
BMI Z-score[c]	0.757 (1.56)
Asthma (yes %)	165 (20.52%)
AHI[d]	3.04 (6.89)
Snoring status[e]	
Never	107 (12.47%)
Rarely	77 (8.97%)
Occasionally	128 (14.92%)
Frequently	184 (21.45%)
Almost always	362 (42.19%)

[a] Some covariates contained missing values, so percentages may not reflect the entire sample.
[b] Due to very small representation of other racial groups, only black and white children were included in this analysis.
[c] BMI refers to body mass index, computed as weight (kg)/height (in)^2. Z-score computation used age norms.
[d] AHI represents apnea-hypopnea index, as described in the manuscript. Log transformed AHI was used for analyses, due to strong positive skew. AHI scores ranged from 0-77.56.
[e] *Rarely* represents an estimate of snoring 1 night per week, *occasionally* 2 nights per week, *frequently* 3 nights per week, and *almost always* ≥4 nights per week.

Table 2. Correlation matrix of behavioral measures.

Measure	CPRS-R hyperactivity	CPRS-R psychosomatic	CPRS-R inattention	CBCL internalizing	CBCL externalizing
CPRS-R hyperactivity	--				
CPRS-R psychosomatic	0.36	--			
CPRS-R inattention	0.73	0.40	--		
CBCL internalizing	0.46	0.63	0.48	--	
CBCL externalizing	0.71	0.39	0.59	0.60	--

Note. All correlations are significant at $p<0.05$

Table 3. Correlation matrix of cognitive measures.

Measure	NEPSY design	NEPSY phon.	NEPSY tower	NEPSY naming	NEPSY arrows	NEPSY v-attn.	NEPSY comp.	DAS verb	DAS nonv
NEPSY design	--								
NEPSY phon.	0.48	--							
NEPSY tower	0.28	0.55	--						
NEPSY naming	0.43	0.34	0.24	--					
NEPSY arrows	0.32	0.33	0.30	0.28	--				
NEPSY v-attn.	0.41	0.39	0.33	0.28	0.29	--			
NEPSY comp.	0.34	0.44	0.43	0.24	0.32	0.30	--		
DAS verbal	0.27	0.31	0.22	0.18	0.20	0.34	0.19	--	
DAS nonverbal	0.50	0.41	0.34	0.33	0.31	0.43	0.32	0.27	--

Note. All correlations are significant at $p<0.05$

Table 4. Baseline covariate significance tests for behavioral outcomes.

Characteristic	□□***deviance***[a]	***df***	***P***
Age	10.74	5	=0.057
Sex	41.21	5	<0.001*
Race	4.27	5	=0.511
BMI	5.66	5	=0.341
Asthma status	19.78	5	=0.001*

[a] reflects change in –2*log likelihood of model containing the covariate relative to the empty model, which includes no covariates.

* covariate is a significant predictor of cognition at $p<0.05$.

Table 5. Predicted behavioral measure change from non-snoring children.

Measure	B (SE) for snoring status group[a]			
	Rarely	Occasionally	Frequently	Almost always
CPRS-R hyperactivity	0.13 (0.16)	0.48 (0.14)*	0.35 (0.13)*	0.40 (0.12)*
CPRS-R psychosomatic	0.41 (0.16)*	0.48 (0.14)*	0.52 (0.13)*	0.50 (0.12)*
CPRS-R inattention	0.15 (0.16)	0.46 (0.14)*	0.37 (0.13)*	0.40 (0.12)*
CBCL internalizing	0.34 (0.16)	0.53 (0.14)*	0.47 (0.13)*	0.58 (0.12)*
CBCL externalizing	0.27 (0.16)	0.43 (0.14)*	0.36 (0.13)*	0.38 (0.12)*

*comparison with *never* snorers is significant following Hochsberg's step-up procedure.
[a] numeric values represent slope coefficients for the predicted change in behavioral measure for snoring group from baseline category of *never* snoring while adjusting for baseline covariates and AHI.
Standard errors are reported in parentheses.

Table 6. Baseline covariate significance tests for cognitive outcomes.

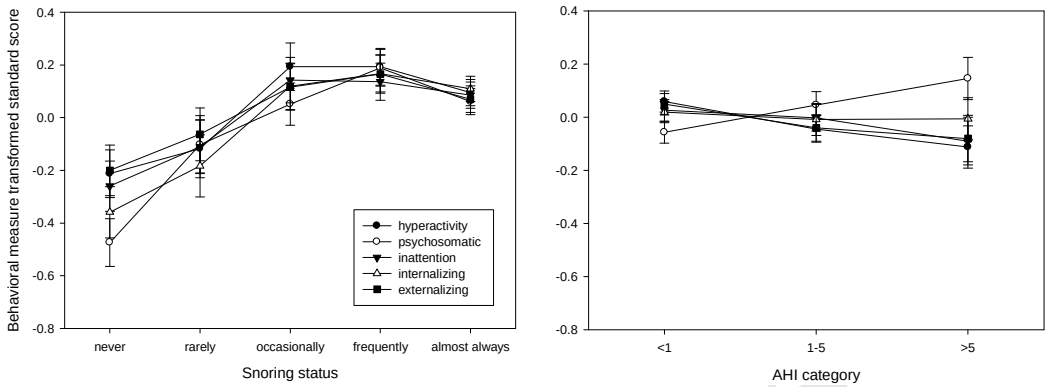
Characteristic	□□***deviance***[a]	***df***	***P***
Age	23.50	9	=0.005*
Sex	68.60	9	<0.001*
Race	101.11	9	<0.001*
BMI	5.33	9	=0.804
Asthma status	27.27	9	=0.001*

[a] reflects change in –2*log likelihood of model containing the covariate relative to the empty model, which includes no covariates.

* covariate is a significant predictor of cognition at $p<0.05$.

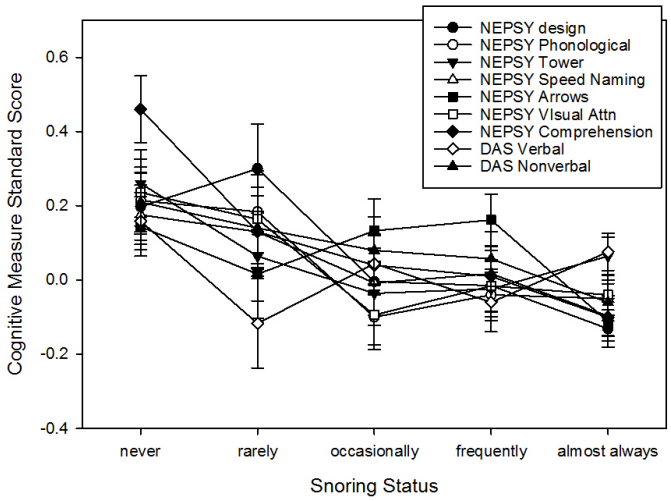
Figures

Figure 1: Behavioral measure scores by snoring and AHI status



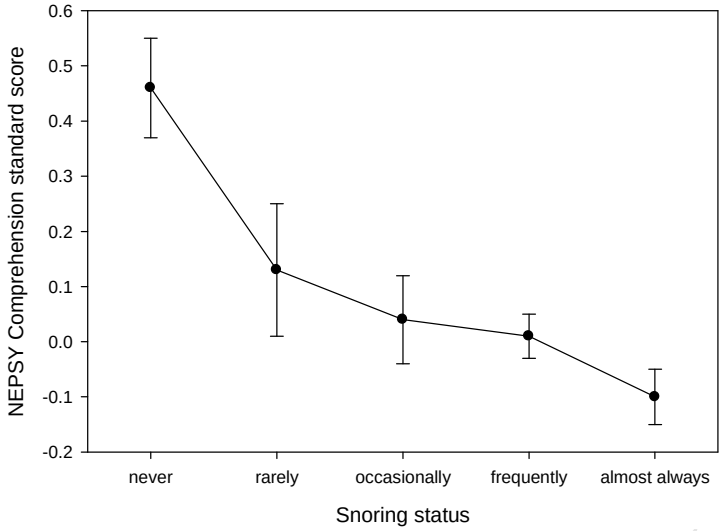
AHI severity categories from sensitivity analyses were used in the right panel for illustrative purposes. Error bars represent standard error.

Figure 2: Cognitive measure scores by snoring status



Error bars represent standard error.

Figure 3: NEPSY Comprehension of Instructions by snoring status



Error bars represent standard error.

Highlights

- Multivariate mixed models examined sleep disordered breathing (SDB) as a predictor of child behavior/cognition.

- Snoring and apnea-hypopnea index (AHI) both significantly predicted the behavioral functioning domain.

- Only snoring significantly predicted overall cognitive functioning.

- Snoring should be independently examined when assessing children with sleep pathology.