



A Mediation Model Linking Body Weight, Cognition, And Sleep Disordered Breathing

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A Mediation Model Linking Body Weight, Cognition, And Sleep Disordered Breathing

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At a Glance Commentary: The independent associations between obesity, sleep disordered breathing, and cognitive dysfunction have been proposed in children but thus far not explored in terms of their mediation. In this study, we report on the multidirectional relationships when studying weight, sleep disordered breathing, and cognitive processing in 351 community children, with either of these conditions serving as a precursor, mediator or outcome. The main findings include that sleep disordered breathing, weight and cognition showed mediator roles in their dependency. The mediator role of weight and sleep disordered breathing is comparable and points towards increasingly adverse outcomes. In contrast, good cognitive abilities might be protective to some extent. Thus, public health campaigns aiming to reduce the risk of obesity and associated morbidities will have to emphasize the health but also the educational benefits in children.

Conflict of interest: The authors have no conflicts of interest to report.

Abstract

Rationale: Academic success involves the ability to use cognitive skills in a school environment. Poor academic performance has been linked to the disrupted sleep associated with sleep disordered breathing (SDB). In parallel, poor sleep is associated with increased risk for obesity, and weight management problems have been linked to executive dysfunction, suggesting that interactions may be operational between SDB, obesity to adversely affect neurocognitive outcomes.

Objective: To test whether mediator relationships exist between body weight, SDB, and cognition.

Methods and Measurements: Structural equation modeling was conducted on data from 351 children in a community-based cohort assessed with the core subtests of the Differential Abilities Scales after an overnight polysomnogram. Body Mass Index, Apnea-Hypopnea Index and cognitive abilities were modeled as latent constructs.

Main Results: In a sample of predominantly Caucasian children, ages 6-10 years, SDB amplified the adverse cognitive and weight outcomes by 0.55 to 0.46 fold, respectively. Weight on the other hand, amplified the risk by 0.39 to 0.40 for SDB and cognitive outcomes. Poor ability to perform complex mental processing functions increased the risk of adverse weight and SDB outcomes by 2.9 and 7.9 fold, respectively.

Conclusion: Cognitive functioning in children is adversely affected by frequent health-related problems, such as obesity and sleep disordered breathing. Furthermore, poorer integrative mental processing may place a child at a bigger risk for adverse health outcomes.

Word count: 224

Key words: Sleep disordered breathing, weight, BMI, cognition, verbal abilities

Introduction

Weight problems in children are a rapidly expanding worldwide health concern. Most studies have thus far primarily focused on the health consequences of childhood obesity, i.e., hypertension, diabetes, or future risk for cardiovascular disease in adulthood, with major efforts being directed towards targeted interventions, such as for example exercise, diet, and school programs.(1, 2) However, there is a paucity of studies aiming to elucidate the contribution of body weight to cognitive functioning. (3-7)

In parallel with the emergence of the obesity epidemic in children, the potential contribution of sleep duration and regularity to the propensity for obesity has increasingly gained attention,(8-10) since short and variable sleep duration appear to be adversely associated with weight and cardiometabolic risks in children.(11-13) In addition, the presence of overweight-obesity is conclusively associated with an increased prevalence of sleep disordered breathing (SDB).(14-18) Interactions between body weight and SDB have recently emerged, whereby the concurrent presence of these 2 health problems adversely impacts dietary preferences and may be particularly detrimental to daily physical activity patterns.(19, 20) Furthermore, increased ghrelin levels support the presence of increased appetite and caloric intake in obese patients with SDB, auxiliary promoting a vicious cycle leading to incremental severity of these 2 underlying conditions.(19, 20) As such, the association between body weight and sleep disorders is becoming increasingly recognized.

Cumulative evidence strongly supports a causal relationship between SDB and neurobehavioral deficits, and a model on executive dysfunction or disruption of prefrontal cortical processes by SDB has been proposed and is widely accepted.(21)

Inattention with collinear behavioral problems and learning problems have been found in children with SDB.(21-26) Notwithstanding such highly concordant findings, the pathogenesis of cognitive and behavioral deficits in SDB patients remains to be fully elucidated. Sleep furthermore plays a fundamental role in learning such as memory and brain plasticity.(27, 28) Similarly, learning processes exert influences on sleep,(29) and both sleep deprivation and chronic sleep restriction impair performance, health and well-being.(30-33)

Therefore, the interrelations between cognitive performance, obesity, and SDB are not only pertinent, but possible, particularly considering the emerging studies on the neuropsychological profile of obese children, which are suggestive of poorer mental flexibility, reduced attention endurance or prolonged reaction time, and poorer school performance and intelligence.(5-7) Also, lower math and reading test scores in obese children have been reported, and furthermore, overweight girls exhibited socio-behavioral problems as well as lower-self esteem.(3, 4) Since some of the cognitive dysfunctions tend to disappear after treatment of obesity, inattention or executive dysfunctions could precede, contribute, or worsen the prognosis of the eating disorder leading to obesity, or alternatively be a consequence of obesity. As such, potential associations between body weight and cognitive performance in children are emerging.

Lastly, we have previously found that sleep disordered breathing is frequently present in poor academic performers, and that treatment of SDB will reverse this problem, at least in part.(34)

Taken together, the findings reported herein raise the hypothesis that complex relationships derived from permutations between sleep, body weight, and cognition are

present. Accordingly, body weight may affect sleep and potentially result in cognitive problems; while sleep may affect body weight and result in similar cognitive problems; or cognitive problems may increase body weight and result in SDB, etc.. In other words, the dependency of any given outcome, namely sleep, body weight and cognition may be mediated. This study was therefore designed to test the hypothesis that mediator relationships of weight, sleep disordered breathing and cognition occur. Our major aim was to quantify and characterize the previous discussed relationships between an independent (e.g., sleep disorder) and a dependent variable (e.g., cognitive function) via the inclusion of a third variable (e.g., weight), i.e., the mediator, to better clarify such relationships.

Methods

Subjects

Data collection for this study was approved by the University of Louisville Human Research Committee and the boards of the participating schools—Jefferson County Public Schools (JCP S) and Archdiocese of Louisville Catholic Schools—from which the community sample was recruited. To screen for eligibility of the participants, parents filled out a sleep questionnaire.(34, 35) On the basis of the completed questionnaires, both non-snoring children and snoring children were randomly selected and invited to participate in the study. Exclusionary criteria for participation in the study included chronic medical conditions, genetic or craniofacial syndromes, developmental delays, a current Individual Education Plan (IEP) at school indicative of significant learning or other difficulties, current use of psychotropic medications, and the presence of an acute infection. Children who did not meet exclusionary criteria according to the questionnaire were invited to the sleep laboratory for overnight polysomnography (NPSG) followed by neurocognitive testing the next morning. Children were tested by trained psychometricians in a quiet room without a parent present. Psychometricians were blind to the child’s sleep study and questionnaire results. Protocols were double-scored by the psychometricians to ensure accuracy.

Measurements

General Cognitive Abilities

Part of the neurocognitive assessment included the Core Subtests of the Differential Abilities Scales (DAS).(36) The DAS is a battery of cognitive tests designed to measure

reasoning and conceptual ability in children, or general cognitive abilities (GCA). The DAS provides individual subtest scores as well as the following composite scores that were analyzed in the current study: Verbal, Nonverbal Reasoning, Spatial, and General Conceptual Ability (GCA). The Verbal Ability cluster (VAB) reflects knowledge of verbal concepts and level of vocabulary development, and it is also indicative of word retrieval from long-term memory. The core subtests administered included Word Definitions, which measures knowledge of word meanings as demonstrated through spoken language or the ability to formulate definition of words (verbal fluency). Similarities measures verbal reasoning and knowledge, where inductive reasoning ability or the ability to relate 3 words to superordinate categories is necessary to earn credit. The Nonverbal Ability cluster (NAB) measures the child's inductive and sequential reasoning abilities. The core subtests are Matrices, measuring nonverbal reasoning, which involves perception and application of relationships amongst abstract figures. Sequential and Quantitative Reasoning involves detection of sequential patterns in figures or numbers. The Spatial Ability cluster (SAB) measures visuospatial construction ability, spatial memory, and spatial reasoning. The core subtests are Pattern Construction that measures nonverbal reasoning and spatial visualization in reproducing designs with colored blocks incorporating response time in the individual scoring, and Recall of Designs involves the short-term recall of visual and spatial relationships through reproduction of abstract figures. The ability score for each subtest is converted to a T score with a mean of 50 and a standard deviation (SD) of 10. The sum of the core subtests is then converted to yield a total standard score for the Ability cluster, with a mean of 100 and a SD of 15. Although the raw scores were used in the modeling procedures, we express standardized composite

scores for descriptive purposes. The DAS was normalized on a large stratified sample of children across the United States and has good validity and reliability.(36) The cluster scores are indicative of the “psychometric g” which is the general ability to perform complex mental processing that involves conceptualization and the transformation of information, (36) and has been considered as a structural correlate to executive function.

Nighttime polysomnography (NPSG)

A standard overnight multichannel polysomnographic evaluation was performed at the Pediatric Sleep Medicine Center. Children were studied for up to 12 hours in a quiet, darkened room with an ambient temperature of 24°C with a parent or guardian present. No drugs were used to induce sleep. The following parameters were measured: chest and abdominal wall movements assessed by inductance plethysmography, heart rate assessed by electrocardiography, and airflow monitored by sidestream endtidal capnography, which also provided breath-by-breath assessments of end-tidal carbon dioxide levels (BCI SC-300; Menomonee Falls, WI), nasal pressure, and an oronasal thermistor. Arterial oxygen saturation (SpO₂) was assessed by pulse oximetry (Nellcor N 100; Nellcor Inc, Hayward, CA), with simultaneous recording of the pulse waveform. Bilateral electro-oculograms, 8 channels of the electroencephalogram, chin and anterior tibial electromyograms, and analog output from a body-position sensor (Braebon Medical Corp, Ogdensburg, NY) were also monitored. All measures were digitized with a commercially available polysomnographic system (Stellate, Montreal, Canada). Tracheal sounds were monitored with a microphone sensor (Sleepmate, Midlothian,VA), and a digital, time-synchronized video recording was obtained.

Sleep architecture was scored by standard techniques.(37) The proportion of time spent in each sleep stage was expressed as percentage of total sleep time (%TST). Central, obstructive and mixed apneic events were counted. Obstructive apnea was defined as the absence of airflow with continued chest wall and abdominal movement for duration of at least two breaths.(38) Hypopneas were defined as a decrease in oronasal flow of >50% on either the thermistor or nasal pressure transducer signal with a corresponding decrease in SpO₂ of >3% or arousal. (38-40) The obstructive apnea/hypopnea index (AHI) was defined as the number of apnea and hypopneas per hour of TST. Arousals were defined according to the American Academy of Sleep Medicine Scoring Manual.(39, 40)

Anthropometric Measurements

Height was measured (to 0.1cm) with a stadiometer (Holtain, Crymych, United Kingdom) and children were weighed (to 0.1kg) with a calibrated scale. Body mass index (BMI) was calculated and the z score was generated using the online BMI z score calculator provided by the Centers for Disease Control and Prevention 2000 growth standards and software (<http://www.cdc.gov/epiinfo/>) (Epi Info [Centers for Disease Control and Prevention, Atlanta, GA]). BMI z scores ≥ 1.65 were considered to fulfill the criterion for obesity, whereas BMI z scores of ≥ 1.04 were defined as overweight and < -1.28 as underweight. A BMI z score falling in between the latter boundaries was considered normal body weight.

Statistical Analysis

Descriptive and correlation analysis were conducted using StatSoft, Inc. (2011, STATISTICA (data analysis software system), version 10. www.statsoft.com, TX). Post-

hoc analyses (unequal N HSD) were conducted for significant group differences. A zero-order correlation matrix was calculated to test the hypothesis that BMI, AHI and cognition were significantly associated.

Structural Equation Modeling (SEM) was conducted using Amos 18 (Amos Development Corporation, FL). SEM is a very powerful multivariate analysis technique that includes specialized versions of a number of other analysis methods as special cases; i.e., causal modeling, confirmatory factor analysis, regression models, covariance structure models and correlation structure models, etc.. SEM offers unique advantages in the assessment of complex interrelated, dependent relationships, while taking measurement errors into account. As a result, one of the strengths of SEM is that the technique models measured and latent (i.e., not measured directly but estimated from several measured variables) variables. Technically, we modeled a mediator variable (M) as being a third variable that links the independent variable (X) to the dependent variable (Y), and thus conveys the effects of X on Y. This recursive mediation model provides two paths feeding into a single dependent variable (Y); the independent (X) and the mediating (M) variable affect the dependent variable (Y), while the independent variable (X) affects the mediator (M). (see Figure 1) All models were fitted through Maximum Likelihood Estimation, bootstrapping (i.e., Critical Ratios for differences between parameters that fall between ± 1.96 are not significant at $p < 0.05$) and 95% bias-corrected confidence intervals; i.e., being less likely to lead to Type I error, having high statistical power, and no requirement of the assumption of normal distribution.(41, 42) Good model fit to the data was evaluated using the CMIN/DF (the relative chi-square) < 1.5 , GFI (Goodness of Fit Index) > 0.9 , RMSEA (Root Mean Square Error of Approximation) < 0.01 (excellent) or 0.05

(good), AIC (Akaike Information Criterion, a comparative measure of fit) being the lower the better by convention. [for more details see SEM handbooks (43)]

For Review Only

Results

Covariates

During the first stages of the study, the Spatial Abilities cluster subtests were not administered to all children, and as a result, only the complete datasets of 351 subjects were used for analyses [55.5% boys and 44.5% girls, 62.6% Non-Hispanic White (WNH) ethnicity, 28.9% African American (AA) ethnicity and 8.6% Other (O) ethnic group]. This group did not differ ($p>0.05$) from the group without the Spatial Abilities cluster on any of the measures of interest.

Mean age was 7.9 ± 0.8 years and the sample had a median obstructive AHI of 0.8/hrTST (Quartile (Q)1: 0.3/hrTST and Q3: 1.7/hrTST; $AHI\leq 1/hrTST$: 57.4% and $AHI>1/hrTST$: 42.6%); median BMI was 17.5 kg/m² (Q1: 15.6 and Q3: 20.8; Underweight: 4.3%, Normal Weight: 45.7, Overweight: 16.1%, Obese: 33.9%). AHI and BMI were associated, such that significantly more obese children had $AHI>1hr/TST$ (18.10% of the total sample) and more normal weight children had $AHI\leq 1/hrTST$ (29.02% of the total sample) [$\chi^2(3)8.6$, $p=0.034$].

Children's GCA was 100.8 ± 13.5 [95% Confidence Interval (CI): 99.4-102.3], with cluster scores being: VAB: 99.4 ± 15.9 (95%CI: 97.8-101.1), NAB: 100.8 ± 13.4 (95%CI: 99.4-102.2), and SAB: 101.9 ± 12.6 (95%CI: 100.6-103.3). No gender differences were found in the cognitive abilities [$F(4,346)=1.5$, $p=0.21$]. African American children exhibited lower abilities (GCA: 95.3 ± 11.5 , VAB: 93.8 ± 13.8 , NAB: 97.07 ± 12.3 , SAB: 97.3 ± 10.6) when compared to the other children [WNH: 103.4 ± 13.6 , VAB: 102.3 ± 16.2 , NAB: 102.3 ± 13.5 , SAB: 104 ± 12.8 , and O: GCA: 100.6 ± 14.3 , VAB: 97.1 ± 15.2 , NAB: 102 ± 14.9 , SAB: 102.6 ± 13.5 ; $F(8,690)=4.6$, $p=0.00002$].

Table 1 shows that AHI and Weight were both independently associated with cognitive problems.

Recursive mediation models

For clarification purposes, each of the models used the same set of variables, that is Age, Gender, Ethnicity, and cognition represented by the raw scores on the VAB, NAB and SAB [denoted as COGN], body weight [denoted as BMI] and sleep disordered breathing [denoted as AHI]. Based on the assumption of ‘imprecision’ in the measurements, COGN, BMI and AHI were therefore entered in the model as latent constructs.

Model 1: The mediator “Sleep Disordered Breathing”

Model 1A identified the mediator role of AHI in the dependence on BMI of COGN outcomes, or how cognition is influenced by weight, with a $\chi^2(12)=11.2$, $p=0.512$ (Table 2). Other significant paths were the indicators of COGN, i.e., at $p<0.001$ for VAB: $\beta=0.67$, NAB: $\beta=0.79$ and SAB: $\beta=0.52$. Age was a significant indicator of BMI ($\beta=3.34$, $p=0.006$), AHI ($\beta=14.09$, $p=0.008$) and COGN ($\beta=14.96$, $p=0.007$). The error variances between Age and SAB ($r=-0.59$, $p<0.001$), Gender and Ethnicity ($r=0.15$, $p=0.011$) and Ethnicity and NAB ($r=0.23$, $p=0.008$) were correlated. The standardized indirect effect between BMI and COGN was -0.11 ± 0.05 with $p=0.009$ supportive of a mediation effect. The model fit was very good. This model is supportive of a substantive mediator role of SDB when having BMI problems towards poorer cognitive performance. Namely, one third of the total impact of BMI on COGN can be ascribed to AHI or in other words, the indirect effect increases the risk 0.55 fold.

Model 1B identified the mediating role of AHI in the dependence on COGN of BMI outcomes with a $\chi^2(9)=13.6$, $p=0.139$ (Table 2). COGN was significantly predicted by VAB: $\beta=0.38$, $p<0.001$ and NAB: $\beta=0.19$, $p<0.001$. Age was a significant indicator of BMI ($\beta=5.62$, $p=0.001$), AHI ($\beta=4.87$, $p<0.001$) and COGN ($\beta=8.25$, $p=0.001$). Each of the clusters' error variances were moderately correlated; i.e., VAB-NAB: $r=0.48$, $p<0.001$ NAB-SAB: $r=0.42$, $p<0.001$, and VAB-SAB: $r=0.32$, $p<0.001$. The error variances between COGN and VAB were weakly inversely related ($r=-0.19$, $p=0.001$). The error variance of VAB was negatively related with Ethnicity ($r=-0.14$, $p=0.003$) and with COGN ($r=-0.19$, $p=0.001$). Gender and Ethnicity error variances were weakly correlated ($r=0.13$, $p=0.01$). SAB error variance was negatively correlated with Ethnicity ($r=-0.11$, $p=0.03$) and Age ($r=-0.41$, $p=0.002$). The standardized indirect effect between COGN and BMI was 0.68 ± 0.19 with $p<0.0001$ and underscored mediation. The model fit was good and indicated that the presence of AHI is detrimental to the impact of COGN on BMI, namely it will increase the risk about 0.46 fold.

Model 2: The mediator "Weight"

Model 2A where BMI mediates the COGN to AHI dependency has a $\chi^2(9)=12.2$, $p=0.200$ (Table 2). COGN was significantly predicted by VAB: $\beta=0.38$, $p<0.001$ and NAB: $\beta=0.21$, $p<0.001$. Age was a significant indicator of BMI ($\beta=4.69$, $p=0.001$), AHI ($\beta=5.71$, $p<0.001$) and COGN ($\beta=8.21$, $p<0.001$). Each of the clusters' error variances were moderately correlated; i.e., VAB-NAB: $r=0.48$, $p<0.001$, NAB-SAB: $r=0.42$, $p<0.001$, and VAB-SAB: $r=0.33$, $p<0.001$. The error variances of VAB with COGN ($r=-0.20$, $p<0.001$) and with Ethnicity ($r=-0.14$, $p=0.003$) were weakly inversely related. SAB error variance was negatively correlated with Ethnicity ($r=-0.11$, $p=0.03$) and Age ($r=-$

0.41, $p=0.002$). Gender and Ethnicity error variances were weakly correlated ($r=0.13$, $p=0.02$). The standardized indirect effect between COGN and AHI was 0.54 ± 0.14 with $p=0.001$, as a result the mediation effect increases the adverse outcome 0.39 fold. The model fit was good. This model shows that BMI plays an increased adverse role.

Model 2B where BMI mediates the AHI to COGN dependency had a $\chi^2(9)=13.5$, $p=0.143$ (Table 2). COGN was significantly predicted by VAB: $\beta=0.30$, $p<0.001$ and NAB: $\beta=0.28$, $p<0.001$. Age was a significant indicator of BMI ($\beta=4.18$, $p=0.001$), AHI ($\beta=3.79$, $p=0.001$) and COGN ($\beta=6.61$, $p=0.001$). Each of the clusters' error variances were moderately correlated; i.e., VAB-NAB: $r=0.48$, $p<0.001$, NAB-SAB: $r=0.42$, $p<0.001$, and VAB-SAB: $r=0.33$, $p<0.001$. The error variances of SAB with COGN ($r=-0.17$, $p=0.001$) and with Ethnicity ($r=-0.11$, $p=0.020$) were weakly inversely related. Gender and Ethnicity error variances were weakly correlated ($r=0.14$, $p=0.013$). VAB error variance was weakly correlated with Ethnicity ($r=-0.13$, $p=0.007$) The standardized indirect effect between AHI and COGN was -0.24 ± 0.09 with $p=0.001$. The model fit was good. This model shows that BMI mediates the impact of sleep disordered breathing on adverse cognitive performance; i.e., 0.40 fold increased risk.

Model 3: The mediator "Cognition"

Model 3A where COGN mediates the AHI to BMI dependency had a $\chi^2(11)=17.5$, $p=0.095$ (Table 2). COGN was significantly predicted by VAB: $\beta=0.30$, $p<0.001$ and NAB: $\beta=0.13$, $p=0.009$. Ethnicity was predictive of AHI ($\beta=2.44$, $p=0.005$) and COGN ($\beta=3.93$, $p=0.014$). Age was a significant indicator of BMI ($\beta=5.59$, $p=0.001$), AHI ($\beta=1.38$, $p=0.001$) and COGN ($\beta=6.61$, $p=0.001$). Each of the clusters' error variances were moderately correlated; i.e., VAB-NAB: $r=0.48$, $p<0.001$, NAB-SAB: $r=0.42$,

$p < 0.001$, and VAB-SAB: $r = 0.32$, $p < 0.001$. The error variances between COGN and VAB were weakly inversely related ($r = -0.19$, $p = 0.003$). SAB error variance was negatively correlated with BMI ($r = -0.19$, $p < 0.001$). AHI and NAB error variances were inversely weakly correlated ($r = -0.11$, $p = 0.01$). Mediation by the standardized indirect effect between AHI and BMI (1.15 ± 0.35 ; $p < 0.001$) is possible. The model fit was adequate. Therefore, cognition will likely adversely mediate the BMI outcome in children with SDB. Namely, it mediates a 2.9 fold increased risk on problematic weight outcome.

Model 3B where COGN mediates the BMI to AHI dependency had a $\chi^2(10) = 16.22$, $p = 0.093$ (Table 2). COGN was significantly predicted by VAB: $\beta = 0.33$, $p < 0.001$ and NAB: $\beta = 0.18$, $p < 0.001$. Age was a significant indicator of BMI ($\beta = 1.87$, $p = 0.007$), AHI ($\beta = 5.76$, $p < 0.001$) and COGN ($\beta = 7.09$, $p < 0.001$). Each of the clusters' error variances was moderately correlated; i.e., VAB-NAB: $r = 0.48$, $p < 0.001$, NAB-SAB: $r = 0.43$, $p < 0.001$, and VAB-SAB: $r = 0.31$, $p < 0.001$. The error variances VAB was inversely related to COGN ($r = -0.28$, $p < 0.001$), and to Age ($r = 0.63$, $p = 0.006$). SAB error variance was negatively correlated with Age ($r = -0.41$, $p = 0.002$). The standardized indirect effect between BMI and AHI was 0.79 ± 0.16 ($p = 0.001$). The model fit was adequate. Cognition completely mediates the detrimental impact of BMI on sleep disordered breathing with a 7.9 fold increased risk. On a closing note, the Standardized Regression Weights can be compared among each other, and the best fitting model can be compared on the AIC in combination with evaluation of the other fit indices.

Discussion

Sleep disordered breathing, weight and cognition showed mediator roles in their dependency. The mediator role of weight and sleep disordered breathing is comparable and points towards increasingly adverse outcomes. In contrast, good cognitive abilities might be protective to some extent.

Before we discuss our findings, several limitations to this study need to be addressed. Children with individual learning programs, mental or medical problems were excluded, such that generalization of our findings is restricted to otherwise normally developing children. Therefore, poor cognitive performance reflects a normal to borderline range, which may dampen some of the mediation relationships studied herein. Similarly, based upon the AHI cut-off, only 35 children had an $AHI > 5/hrTST$. In other words, more severe SDB cases may alter the magnitude of the mediation effects reported here. All children were assessed the morning after their sleep study or 7.9 ± 0.7 hours of sleep. This is important since sleep deprivation in the nights preceding cognitive testing may adversely affect performance. In addition, even though a full discussion on the operationalization of the applied cognitive test is not within the scope of this study, the cognitive battery of tests effectively assesses both conceptual and reasoning abilities, thereby reflecting a variety of separate and distinct areas of cognitive functioning. To simplify the modeling procedures and to verify our hypothesis, we chose to use the raw cluster scores, and not the individual test scores. Finally, some relaxation in the a priori assumptions was needed as part of the modeling procedures.

A child's progress in school is closely related to its cognitive strengths and weaknesses. As a result, measures of general cognitive abilities are often the reference

point towards academic achievement and success in life. Since sleep is correlated to daytime performance such as learning, its role has thus far been vastly underestimated. In the current study, we focused on SDB and increased BMI as two highly prevalent and potentially interdependent health problems.(44) Likewise, compromised health may affect learning abilities in children. In fact, cognitive processing might precede, contribute, or worsen health conditions, and vice-versa. However, our findings were specifically restricted to general cognitive abilities and integrative processing, and therefore future studies on more specific neuropsychological functioning may shed light to the precise impact of compromised health in specific cognitive domains. Significant neurocognitive and neurobehavioral deficits have been associated with SDB throughout the recent decades with inattention and executive dysfunction being repeatedly reported. (21, 25, 26, 45) In general, the current obesity epidemic could further amplify the association between cognition and SDB in children. Unfortunately, the role of obesity has not been specifically addressed despite being a common and highly prevalent condition in the pediatric population, with a median incidence of obesity in the 10% to 12% range.(40)

Our findings concur with emerging reports of diminished cognitive performance with increasing BMI. (6, 7, 46) In fact, there is a 0.55 fold increased risk of poorer abilities that is mediated by SDB [model 1A]. Thus, the presence of SDB in overweight and obese children will increase their risk for decreased cognitive performance, and therefore, these findings would justify appropriate screening for this adverse outcome. Conversely, the structural and functional differences in the brain of children with SDB have yet to be examined. However, in children with congenital central hypoventilation

syndrome, a genetic disorder characterized by sleep disordered breathing, evidence of localized injury in hippocampal areas has emerged.(47) In adults, preliminary neuroimaging-derived neural correlates in patients with SDB suggest that atrophy of the hippocampus and white matter lesions in the frontal lobes are present, along with widespread neural differences in motor, sensory, and autonomic brain regions.(48) Thus, imaging studies in both obese and non-obese children with and without SDB are urgently needed to gauge the impact of these conditions on the CNS, particularly considering our findings, whereby a 0.46 fold increased impact of cognitive processing on weight was mediated by SDB [model 1B]. This finding would therefore promote screening for SDB in poorly performing children, and evidence to this effect was reported among academically-failing young children.(34) Thus, based on our findings, implementation of screening for sleep disordered breathing in children with overweight and/or scholastic difficulties is advocated in the clinical setting.

Similarly, weight plays a comparable mediator role. Alterations in brain morphology especially in the frontal lobe areas have been reported in clinically overweight to obese young adults. (49) In fact, reduced focal grey matter volume and enlarged orbitofrontal white matter found in these adults with elevated BMI would suggest that potential structural changes in a developing brain may not only be present, but further accentuated. In adults, diffusion tensor imaging indicated that increasing BMI was independently associated with lower fractional anisotropy in the genu, splenium, and fornix, and a BMI-age interaction emerged in the splenium and body of the corpus callosum.(50) These brain regions are critically important pathways for integrative processing and undergo myelination through childhood and adolescence. The observation

in our models that chronological age was significantly predictive towards each of the 3 variables, i.e., AHI, BMI, and cognition, may potentially underscore the importance of development as a particularly vulnerable stage. Further, specific craniofacial features that appear to influence brain development (51) may also predispose to SDB. In other words, neurological aspects of intrinsic brain functioning may contribute to the pathophysiology of SDB,(52) in which BMI likely increases risk. In fact, the intriguing part regarding model 1B as described here is that assuming neurological problems precede SDB, then the impact of SDB on weight is not significantly different from the neurological (or cognitive) impact on weight. However, both BMI and neurological function will have an independent significant impact on SDB [model 1B and 2A/3A especially]. It would be pure speculation to contemplate any specific pathophysiological mechanisms based on the present study. However, we can forcefully point out that SDB affects cognitive outcomes (as shown by other studies), but also point out that the presence of BMI problems will adversely impact such relationships, particularly during a period where our brain is rapidly developing. Our models are indeed suggestive for intricate interdependencies in the mediation between BMI, SDB, and cognition.

During childhood, developmental stage can be expressed as for instance chronological age, developmental age and physical maturation which do not necessarily develop in synchrony, and are considered to reflect the interplay of nature and nurture. As mentioned, chronological age played a substantial role towards each of the measures of interest in all models, as well as an intriguing residual variance association of spatial abilities and age, suggesting that the nature of the tests used,(53) or lower socioeconomic status, (54) unfamiliarity (55) and other factors may account for this finding. Namely,

spatial processing skills are an important component in learning, and thus, in cognitive development. Cognition was comparably predicted by verbal and nonverbal abilities except when cognitive outcome depended on weight when mediated by SDB. In the latter, a more widespread dysfunctional pattern was found. Considering that a 0.48 point decrease in grade-point-average was found for children in grade 7-9 when becoming overweight (not found for children in grades 3-6), and a two-fold likelihood of low grades in overweight children (7) the impact of the developmental stage at which either sleep disordered breathing, weight and cognition problems occur warrants further exploration. In addition, in future studies similar modeling incorporating systemic inflammatory markers may improve the performance of the models presented herein.(56)

In summary, multidirectional relationships were found when studying SDB, BMI, and cognitive processing in community children, with either of these elements serving as a precursor, mediator or outcome. Since only rough indicators of these conditions were modeled, i.e., AHI, BMI, and COGN, we specifically opted for unobserved latent constructs allowing residual variances, and accordingly less stringent interpretations are possible. Notwithstanding, careful consideration of the mediation findings reported should serve as indicators of the unique importance of sleep integrity and normal somatic to foster brain plasticity.

List of Abbreviations

COGN: cognition

BMI: body mass index

SDB: sleep disordered breathing

AHI: Apnea-Hypopnea Index

GCA: general cognitive abilities

VAB: Verbal Ability cluster

NAB: Nonverbal Ability cluster

SAB: Spatial Ability cluster

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Tables and Figures

Table 1: Zero-order correlation matrix of the variables of interest

Table 2: Mediation Models for Weight, Sleep Disordered Breathing and Cognition

Figure 1: Scheme of a mediation model

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Table 1: Zero-order correlation matrix of the variables of interest

	Age	AHI	BMI	GCA	VAB	NAB	SAB
Age	1						
AHI	0.00	1					
BMI	0.22	0.22	1				
GCA	0.07	-0.16	-0.11	1			
VAB	0.10	-0.13	-0.12	0.82	1		
NAB	0.12	-0.18	-0.08	0.83	0.50	1	
SAB	-0.07	-0.07	-0.07	0.77	0.43	0.54	1

AHI: Apnea-Hypopnea Index, **BMI:** Body Mass Index, **GCA:** General Cognitive Abilities,

VAB: Verbal Abilities, **NAB:** Nonverbal Abilities, **SAB:** Spatial Abilities

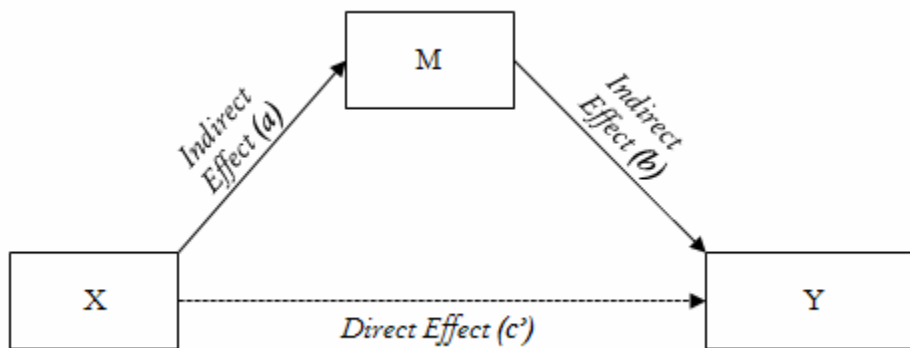
In bold significant results at <0.05

Table 2: Mediation Models for Weight, Sleep Disordered Breathing and Cognition

model	X	M	Y	a		b		c'		Critical Ratios			Fit	
				$\beta \pm S.E.$	p-	$\beta \pm S.E.$	p-	$\beta \pm S.E.$	p-	a-b	a-c'	b-c'	CMIN/DF	RMSEA
				95% CI	value	95% CI	value	95% CI	value				GFI	AIC
1A	BMI	AHI	COGN	0.12 ± 0.05	0.012	-0.96 ± 0.02	<0.001	-0.20 ± 0.04	<0.001	-7.72	-8.07	2.62	0.9	0.00
				0.03 to 0.22		-0.99 to 0.93		-0.28 to -0.11					0.99	59.2
1B	COGN	AHI	BMI	-0.77 ± 0.08	<0.001	-0.88 ± 0.17	<0.001	-1.49 ± 0.16	<0.001	-18.07	21.10	-0.35	1.5	0.038
				-0.88 to -0.60		-1.23 to -0.58		-1.85 to -1.22					0.99	67.6
2A	COGN	BMI	AHI	-0.73 ± 0.05	<0.001	-0.74 ± 0.15	<0.001	-1.39 ± 0.10	<0.001	-15.78	-19.71	4.72	1.3	0.032
				-0.80 to -0.60		-1.09 to -0.56		-1.62 to -1.25					0.99	66.2
2B	AHI	BMI	COGN	0.41 ± 0.16	0.036	-0.58 ± 0.07	<0.001	-0.60 ± 0.08	<0.001	6.52	6.34	2.68	1.5	0.038
				0.26 to 0.54		-0.65 to -0.53		-0.66 to -0.52					0.99	67.5
3A	AHI	COGN	BMI	-0.88 ± 0.11	<0.001	-1.31 ± 0.27	<0.001	-0.39 ± 0.26	<0.001	3.41	-3.44	1.78	1.5	0.041
				-0.98 to -0.57		-1.85 to -1.09		-0.89 to -0.18					0.99	67.5
3B	BMI	COGN	AHI	-0.74 ± 0.14	<0.001	-1.07 ± 0.07	<0.001	-0.10 ± 0.13	0.055	-3.45	-3.69	4.18	1.6	0.042
				-0.93 to -0.44		-1.19 to -0.88		-0.27 to 0.18					0.98	68.2

a, b, c are Standardized Regression Weights with Standard Error (S.E.), **BMI:** Body Mass Index (or Weight); **AHI:** Apnea-Hypopnea Index (or Sleep Disordered Breathing);

COGN: Cognition predicted by raw scores of VAB (Verbal Abilities cluster), NAB (Nonverbal Abilities cluster) and SAB (Spatial Abilities cluster)

Figure 1: Scheme of a Mediation Model

Conventionally the path X to Y (without M) is the total effect (c) being the Direct Effect (c') + the Indirect Effect (ab).