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Cognition, sleep and respiration in at-risk children treated for obstructive sleep apnoea

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ABSTRACT: Sleep-disordered breathing in children has been associated with cognitive impairment. The purpose of this study was to examine the impact of tonsillectomy and adenoidectomy (T&A) on sleep, respiration and cognitive function in children of pre-school age with obstructive sleep apnoea (OSA) from a low-income community population.

Altogether, 19 children attending state-funded pre-school programmes underwent overnight polysomnography and cognitive assessment before and following surgical treatment for OSA; 19 matched controls were also assessed.

Following T&A, OSA subjects' delta sleep increased, rapid eye movement sleep decreased, and respiratory and arousal indices improved. There were no significant differences in OSA subjects' post-operative sleep or respiratory measures compared to controls. Prior to T&A, cognitive scores were significantly lower in OSA subjects *versus* controls; following T&A, OSA subjects' scores improved compared to pre-operative scores and did not differ from those of matched controls.

Following tonsillectomy and adenoidectomy, at-risk pre-schoolers recruited directly from the community showed normalised sleep and respiratory patterns and improved cognitive scores. These findings, in this uniquely vulnerable population, which is unlikely to seek evaluation and treatment for obstructive sleep apnoea, underscore the potential value of outreach screening programmes for sleep-disordered breathing, particularly among low-income groups of pre-school age.

KEYWORDS: Cognition, development, obstructive sleep apnoea, respiration, sleep

The prevalence of habitual snoring in otherwise healthy children varies geographically and has been reported to be 6–27% [1–3]. Snoring is the cardinal symptom of sleep-disordered breathing (SDB), which encompasses obstructive sleep apnoea (OSA) and upper airway resistance syndrome [4]. SDB may be present in up to 3% of children and is associated with sleep fragmentation and gas exchange abnormalities. Children with SDB are more frequent users of healthcare services [5], experience more frequent comorbid chronic illnesses [1, 6], may develop significant clinical cardiovascular morbidity [7] and also display daytime behavioural manifestations, including attention deficit/hyperactivity disorder [8, 9], as well as other psychiatric and behavioural comorbid conditions [10–12]. In addition to cardiovascular and behavioural complications, SDB in children has been associated with impairment of normal cognitive development [8, 13] and school performance [2, 14, 15].

The preferred treatment for OSA in otherwise healthy children is tonsillectomy and adenoidectomy (T&A) [16, 17]. Although T&A may not be universally effective in paediatric patients [18], several studies have shown that post-operative recovery from OSA treated with T&A includes normalisation of sleep and respiratory measures [16, 17, 19–21], and improvements in school performance [2], cognitive function [13, 22, 23], behaviour [24] and quality of life [25, 26].

Thus, the cumulative evidence indicates that paediatric SDB is a frequent condition leading to significant clinical morbidity and that treatment for OSA in paediatric populations leads to improvements in clinical outcome, including cognitive function. Taken together, these studies support the need for early intervention. However, most studies on the reversibility of cognitive function deficits have been restricted to

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small clinically referred populations encompassing a broad age range. The goal of the present study was to examine the impact of T&A in young children with OSA recruited from a highly vulnerable at-risk community population, who had not previously sought medical evaluation for the potential presence of SDB.

METHODS

The study was approved by the Institutional Review Boards of the University of Louisville and Norton Healthcare (both Louisville, KY, USA); informed consent was obtained separately for participation in the parental report questionnaire and overnight polysomnography (PSG) elements of the study.

Questionnaire instrument

The information collected included the demographics of both parents and the child, and child behaviours, including frequency and loudness of snoring. Report options for snoring frequency included: never (never in the past 6 months), rarely (once a week), occasionally (twice weekly), frequently (three or four times a week) and almost always (more than four times a week). Subjects whose parents indicated that snoring occurred occasionally or more frequently were contacted by telephone and invited to participate in the second phase of the study, including overnight PSG and cognitive assessment. This instrument has previously demonstrated a high sensitivity when used in the same population [27].

Participants

Subjects attended state-sponsored Early Jump Start pre-school programmes, admission to which is limited to children who are disadvantaged either developmentally, as determined through an Individual Education Plan, or financially. Families fulfilling the latter criterion must be financially eligible for the National School Lunch Program. For a family of four, the maximum gross annual household income for eligibility during the initial year of the study was US$22,945; the national poverty level during this period was $18,400. During the academic years studied, 91% of children were admitted to Early Jump Start on the basis of family income eligibility (D. Corson, Assessment, Research, and Planning, Jefferson County Public Schools, Louisville, KY, USA, personal communication). Questionnaires were sent home with all children enrolled in Early Jump Start pre-school classes, to be completed by the parent(s) and returned to school, where they were collected by a researcher. The subjects who were invited to participate further in the study were those admitted to Early Jump Start programmes based upon financial eligibility; survey participants who were developmentally disadvantaged or who had overt craniofacial abnormalities and whose survey indicated risk for SDB were referred to the affiliated sleep medicine clinic.

Qualifying subjects were recruited for overnight PSG assessment based on parental reported questionnaires previously validated using the same population [27]. Subjects who were subsequently diagnosed with OSA and who underwent T&A were invited to return for follow-up assessments.

Control subjects

Classmates from the same socio-economically at-risk population whose survey results indicated that they had no history of snoring were matched to the OSA subjects on the basis of age (median of the OSA subjects' pre- and post-operative assessment ages), as well as sex, ethnicity and highest level of maternal education achieved (table 1). These matched controls underwent PSG and cognitive testing on a single occasion. Repeat testing was not administered to the matched healthy controls.

Overnight polysomnography

Subjects were excluded from this phase of the investigation on the basis of incomplete questionnaires and/or contact information, chronic medical conditions, and genetic or overt craniofacial abnormalities, and/or when they had already sought medical evaluation for snoring. No PSG was performed on a night on which a child was acutely ill.

A standard overnight multichannel PSG evaluation was performed in the Sleep Medicine Center at Kosair Children's Hospital (Louisville, KY, USA). Children were studied for up to 12 h in a quiet darkened room with an ambient temperature of ~24°C with a parent or guardian present. Lights out was 21:32 h (SD 19.1 min) and lights on was 06:20 h (SD 13.0 min). No medications were used to induce sleep.

The following parameters were measured: chest and abdominal wall movement by respiratory impedance or inductance plethysmography; cardiac frequency by ECG; and airflow with a side-stream end-tidal capnograph (BCI SC-300; Redding Medical, Inc., Finksburg, MD, USA), which also provided breath-by-breath assessment of end-tidal carbon dioxide tension (P_{ET,CO_2}) and nasal pressure, and an oral–nasal airflow thermistor. Arterial oxygen saturation measured by pulse oximetry (S_{p,O_2}) was assessed (Nellcor N 100; Nellcor, Inc., Hayward, CA, USA), with a simultaneously recorded pulse waveform. A bilateral electro-oculogram, eight channels of

TABLE 1 Demographics and maternal characteristics of children before and after adenoidectomy and tonsillectomy, and of matched controls

	Before	After	Control
Subjects n	19	19#	19¶
Age yrs			
Questionnaire completion	4.2±0.77	4.2±0.77#	4.3±0.67
PSG	4.4±0.70	4.9±0.70	4.5±0.64
Males %	53	53#	53¶
Ethnicity %			
Caucasian	32	32#	32¶
African-American	58	58#	58¶
Asian/Pac. I. or other	10	10#	10¶
Maternal education %			
Junior high school	5	5#	5¶
High school	68	68#	68¶
College	21	21#	21¶
Graduate school	5	5#	5¶

Data are presented as mean±SD or percentages. PSG: polysomnography; Pac. I.: Pacific Islander. #: value unchanged post-operatively; ¶: controls matched on this variable: no difference.

electroencephalogram, chin and anterior tibial electromyograms, and analogue output from a body position sensor (Braebon Medical Corporation, Ogdensburg, NY, USA) were also monitored. All measures were digitised using a commercially available PSG system (MedCare Diagnostics, Buffalo, NY, USA). Tracheal sound was monitored with a microphone sensor (Sleepmate; Rochester Electro-Medical, Inc., Tampa, FL, USA) and digital synchronised video images were collected.

Sleep and respiratory characteristics

Sleep architecture was assessed using standard techniques [28]. Central, obstructive and mixed apnoeic events were scored using changes measured with an oral–nasal thermistor and/or end-tidal carbon dioxide cannula. Obstructive apnoea was defined as the absence of airflow with continued chest wall and abdominal movement for at least two breaths [29, 30]. Hypopnoeas were defined as a decrease in nasal flow of $\geqslant$50% with a corresponding decrease in S_{p,O_2} of $\geqslant$4% and/or arousal [30]. The apnoea/hypopnoea index (AHI) was defined as the number of apnoeas and hypopnoeas per hour of total sleep time (TST). For treatment referral purposes, only patients with an obstructive AHI of >5 events·h^{-1} were considered as candidates for T&A and referred for surgical intervention. Mean S_{p,O_2} and S_{p,O_2} nadir were determined. The mean and peak P_{ET,CO_2} were determined. Since criteria for arousal have not yet been developed for children [31], arousals were defined as recommended by the American Sleep Disorders Association Task Force report [32], and included respiratory-related (occurring immediately subsequent to an apnoea, hypopnoea or snore), technician-induced and spontaneous arousals. Respiratory arousal index was expressed as the total number of respiratory-related arousals per hour of TST; total arousal index was expressed as the number of combined arousals per hour of TST.

Cognitive assessments

At 08:00 h on the morning following PSG and lasting ~45 min, developmentally appropriate cognitive assessments were administered. The Differential Ability Scales (DAS) [33], a measure of general conceptual ability (GCA), were administered. The pre-school version is intended for use with children between 2 yrs 6 months and 5 yrs 11 months of age, and has attractive graphics that are appealing and engaging for pre-school children. Assessments of verbal (verbal comprehension and naming vocabulary) and nonverbal ability (picture similarities, pattern construction, copying and early number concepts) and block building were administered. Scores are reported as standard scores with a mean$\pm$SD of 100$\pm$15.

The Pre-Reading Abilities subtests from the Developmental Neuropsychological Assessment (NEPSY) [34] were used to obtain measures of phonological processing, sentence comprehension and naming. This scale has been standardised for use with children aged 3–12 yrs. Scores are reported as subtest scaled scores with a mean$\pm$SD of 10$\pm$3.

Examiners were blinded to subjects' diagnostic status and different reliable examiners performed post-operative assessments.

Statistical analyses

Repeated-measures ANOVA (general linear model) was used to test for significant differences between pre- and post-treatment sleep, respiratory and cognitive measures, as well as between OSA subjects' pre- and post-treatment measures compared to matched controls. A p-value of $\leqslant$0.05 was considered significant. With 19 subjects and a difference in SD of 0.5 between DAS scores significant when one-tailed α was 0.05, the statistical power of the study was 0.83.

RESULTS

Characteristics of sample population

There were 1,951 respondents to the questionnaire during the combined 2001 and 2002 academic years, which represented a response rate of 32.8%. The ethnic distribution of those who responded to the survey (table 1) was similar to that of the general pre-school population during the same academic years (D. Corson, personal communication).

Between October 2001 and June 2003, 273 pre-schoolers underwent PSG and cognitive testing. Of these, 39 were diagnosed as having SDB, and it was recommended by the medical director of the study that the family discuss referral for surgical treatment with the child's primary care physician. Of these 39, nine families could not be contacted to determine treatment status despite repeated attempts, five had not followed treatment recommendations within 13 months and the remaining 25 were known to have undergone T&A. Of the 25 who received treatment, five repeatedly did not attend follow-up appointments, and one refused to participate a second time (fig. 1). Thus 19 children underwent T&A (between 23 days and 8.1 months following initial PSG (mean$\pm$SD 2.9$\pm$2.1 months)) and returned for post-operative evaluation 2.9–6.3 months (4.0$\pm$1.0 months) following surgery, completing all phases of the study, and were therefore available for analysis (table 1). The time from initial PSG and cognitive assessment to the follow-up for these OSA subjects was 6.9$\pm$2.3 months.

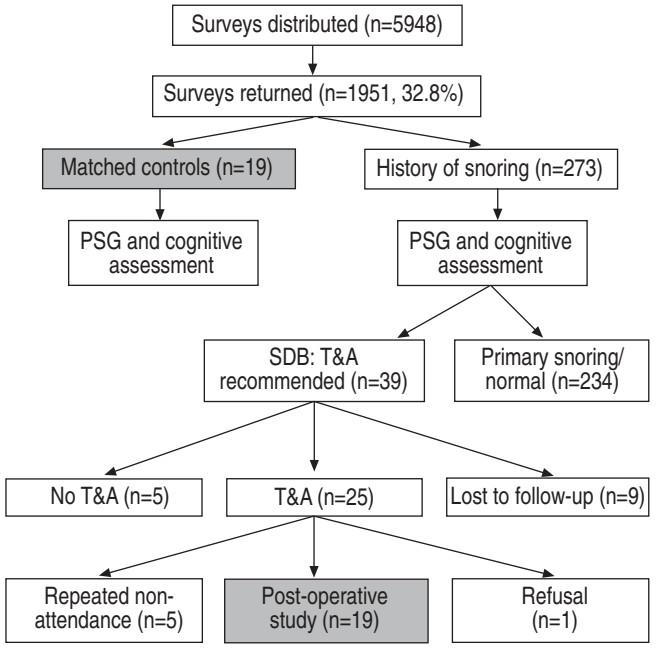

FIGURE 1. Subject and matched control recruitment. PSG: polysomnography; SDB: sleep-disordered breathing; T&A: tonsillectomy and adenoidectomy.

Sleep architecture and respiratory measures

Following T&A, the percentage of delta sleep increased and that of rapid eye movement (REM) sleep decreased in OSA subjects. Compared to controls, the pre-operative percentage of time awake and of delta sleep were reduced. Following T&A, respiratory arousal index, total arousal index, AHI and apnoea index were all improved. There were no significant differences between OSA post-operative sleep or respiratory measures and those of controls (table 2).

Cognitive function

Prior to T&A, DAS scores were significantly lower in OSA subjects than in controls (table 3). Following T&A, OSA DAS scores improved significantly compared to pre-operative scores and did not differ from those of the matched controls (table 3). Sixteen of the 19 OSA subjects improved their GCA scores post-operatively by one to 22 points (mean±SEM 6.9±1.4) The scores of three OSA subjects decreased post-operatively by five (two) to nine (one) points.

Cognitive assessments were administered to all subjects. DAS GCA scores were obtained for all; six pre-operative, one post-operative and five control administrations resulted in GCA being pro-rated due to a single missing subtest. Thus the data for individual verbal and nonverbal subtests were not compared for post-operative improvement analysis due to insufficient statistical power.

Since this population of children was very difficult to assess due to their young age and developmentally at-risk status, NEPSY subtest results were sometimes unavailable for analysis due to administration difficulties. As a result, data on only 11, 15 and 18 subjects were available for pre-/post-operative comparisons for phonological processing, sentence repetition and verbal fluency, respectively. NEPSY scores were not found to change or differ from controls on any measure except for verbal fluency (OSA subject scores were consistently lower than those of controls both before and after T&A).

DISCUSSION

The present at-risk population cohort of children with OSA, who were matched to a control group for median age between the initial and follow-up assessment, sex, ethnicity and maternal education, showed normalisation of their sleep and breathing patterns and improved cognitive scores following surgical treatment. The current sample was recruited directly from the community and represents a unique and especially vulnerable population that is ordinarily unlikely to seek evaluation and treatment for SDB. The current study underscores the potential value of outreach screening programmes for SDB, particularly within low-income groups of pre-school age.

The OSA subjects in the present community-recruited study showed sleep architecture improvements post-operatively; namely, their latency to sleep onset decreased and the percentage of time spent in delta sleep increased. These findings are inconsistent with the only previously reported clinical trial reporting sleep stage percentages before and after T&A, in which no significant changes in overall sleep stage percentages were found [21]. Since a developmental trajectory exists for changes in sleep stage percentage distribution throughout the night, the present authors suspect that, although the number of subjects included in the present study was relatively low, the narrow age range included in the present cohort is likely to have afforded greater statistical

TABLE 2 Polysomnographic characteristics of children with sleep-disordered breathing before and after tonsillectomy and adenoidectomy, and of matched controls

	Before	After	p-value	Control	p-value#
Subjects n	19	19		19	
Sleep efficiency %	90.0±0.01	93.0±0.01		89.0±0.01	
Sleep latency min	31.5±6.8	18.4±3.6	0.029	27.2±6.5	
REM latency min	84.3±9.7	76.6±4.0		81.5±9.1	
Awake %¶	6.7±1.1	7.4±1.0		10.6±1.4	0.033
Sleep stage %+					
1	5.9±0.74	4.9±0.32		5.6±0.70	
2	45.6±2.0	43.2±1.1		38.8±1.8	
Delta	23.5±1.5	28.8±1.5	0.014	29.9±1.3	0.010
REM	25.0±0.98	22.1±0.74	0.003	24.7±1.20	
Total sleep time min	473.8±9.11	487.6±8.53		467.3±8.58	
Spontaneous arousal index	6.3±0.81	7.3±0.44		7.7±0.52	
Respiratory arousal index	7.3±2.7	0.42±0.13	0.022	0.20±0.06	0.017
Total arousal index	14.5±2.5	8.0±0.23	0.014	8.3±0.52	0.033
Apnoea/hypopnoea index	10.1±2.9	1.0±0.23	0.006	0.6±0.19	0.004
Apnoea index	5.8±1.8	1.0±0.23	0.015	0.8±0.19	0.010
Baseline S_{p,O_2} %	97±0.46	98±0.23		98±0.23	
S_{p,O_2} nadir %	82±2.8	92±0.91	0.004	94±0.69	0.001

Data are presented as mean±SEM. REM: rapid eye movement; S_{p,O_2}: arterial oxygen saturation measured by pulse oximetry. #: control *versus* pre-operative value; ¶: calculation based on time from lights out to lights on; +: calculation based on total sleep time.

TABLE 3 Differential Ability Scales performance in children with sleep-disordered breathing before and after adenoidectomy and tonsillectomy, and in matched controls

	Before	After	p-value#	Control	p-value#	
					1¶	2+
Score§	82.52±14.03	87.16±14.65	0.02	93.95±24.93	0.01	0.13

Data are presented as mean±SD. #: 18 degrees of freedom; ¶: *versus* pre-operative score; +: *versus* post-operative score; §: standard score=100±15.

power, and therefore permitted identification of significant improvements in sleep architecture after T&A.

An alternative possibility could include a greater propensity for SDB-induced disruption of sleep architecture in socio-economically at-risk paediatric populations, such that surgical correction of SDB could result in increased differences between pre- and post-operative sleep characteristics. Notwithstanding such considerations, when the post-operative sleep measures of OSA subjects were compared with those of controls matched for socio-economic factors, a complete normalisation of sleep measures was found, to the extent that there were no longer significant differences from matched controls.

The decrease in the percentage of REM sleep following treatment for OSA in the present study was unexpected and in conflict with previously published data showing that an increased percentage of REM sleep is associated with improvements in both DAS and NEPSY scores in a slightly older broad community sample [8]. However, the percentage of REM sleep of OSA subjects did not differ from that of control subjects pre- or post-operatively. Although significant, the percentage difference between pre- and post-operative percentages of REM sleep in the current study translates to a relatively low mean difference in absolute duration of REM sleep (3.4 min). Regardless, this discrepancy emphasises the need for more intensive study of the relationship between sleep and neurocognitive function in young children who are at-risk and otherwise.

Arousal measure indices also normalised among the at-risk children in the OSA group after surgery. Indeed, the total arousal index was almost halved post-operatively; this was accounted for by the almost complete abrogation of respiratory arousals. In contrast, the spontaneous arousal index did not differ post-operatively, and nor did values for either the pre- or post-operative measures differ from those of matched controls. Despite the high variability in the scoring criterion for arousal among different centres, the post-operative reduction in the respiratory arousal index in the present study was consistent with previous findings from available clinical trials [17, 21].

As expected, and previously reported [16, 17, 19–21], marked pre-to-post-surgical changes in respiratory indices during sleep were found. Both the AHI and apnoea index were reduced after T&A, and no longer differed from those of matched controls. These findings further corroborate the relatively high short-term efficacy of T&A in paediatric OSA [18]. Blood oxygenation in the absence of any respiratory events (baseline S_{p,O_2}) did not differ pre- and post-operatively or compared to controls subjects; S_{p,O_2} nadir improved pre-to-post-surgically, was lower prior to surgery compared to controls and did not differ from controls following surgery.

Concurrent with changes in sleep, arousal and respiratory measures, improvements in cognitive function measures were identified, with normalisation of complex mental functions after T&A compared to matched controls, as measured by the DAS. These findings are particularly encouraging since children in the current sample were already at high risk of reduced capacity in performing complex mental functions due to their low socio-economic status and environmental impoverishment. Both the sleep fragmentation and abnormal blood gas exchange that ensue from upper airway obstruction during sleep in OSA may induce substantial alterations in brain function and structure in general [35], and, more specifically, affect the prefrontal cortex, leading to impairments in cognitive and executive functional processing [36]. However, the present study suggests that these cognitive impairments may be reversible in very young children upon efficacious treatment.

As mentioned above, there is a paucity of information on the reversibility of cognitive morbidity associated with paediatric SDB. However, animal models have revealed long-term partially irreversible impairments in learning, memory and executive function, when the intermittent hypoxia that characteristically accompanies SDB occurs early in development [36–40]. Interestingly, environmental enrichment reduces the susceptibility to cognitive dysfunction following exposures to intermittent hypoxia during sleep [41]. It could be argued that environmental impoverishment would enhance the deleterious effects of SDB. Indeed, in the present study, the mean DAS scores for OSA subjects' post-operative assessments remain below the standard means, as do those of the matched control subjects. Thus the present authors submit that socio-economically challenged paediatric populations who do not have access to environments that are conducive to optimal learning and brain development opportunities prior to the onset of the intermittent hypoxia associated with OSA may be particularly susceptible to the deleterious effects of this disorder.

Limitations

There are several potential limitations to the present study. Attempts were made to administer components of the NEPSY. However, administration of a relatively large battery of tests to such young children is fraught with substantial difficulties, particularly as regards achieving the necessary sustained attention and motivation to successfully and reliably complete such tests. Thus several of the children enrolled in this study were unable to complete the last few items of the NEPSY,

leading to insufficient statistical power in the comparative analyses of these subtests. Future studies assessing similar populations may benefit from a school-based assessment approach in which testing is administered over a series of days rather than in a single session.

The assessments used are designed to be stable over time, but, because the OSA subjects were tested twice, improvements due to practice effects should be considered. The DAS manual states that ''we must keep practice effects in mind when interpreting the scores of a child retested within a few months of initial testing'' (p. 184) and further adds that GCA has been shown to vary by approximately three points due to practice effects [33]. Since OSA subjects' initial and follow-up assessments were separated by 6.9 ± 2.3 months (mean $\pm$ SD), this was sufficient to nullify this concern.

A related limitation was that, among this at-risk population, it proved difficult to find families willing to participate as control subjects and impossible to expect them to return for a follow-up assessment. As such, cognitive assessments were administered to the control subjects on a single occasion, whereas the OSA subjects were tested twice. Since all subjects were enrolled in a pre-school programme designed to provide an enriching academic experience, it is possible that both OSA and control subjects alike may have shown improvements in their cognitive scores over time. In view of this potential confounder, controls were matched to the intermediary age between the pre- and post-operative assessments of the OSA subjects, such that the groups could be compared since the beneficial effects of the academic programme would apply to both OSA and control subjects.

It is possible that the subjects participating in the present study were vulnerable to first-night effects, and that these may have masked post-operative changes in sleep efficiency, a particular concern when the number of subjects is relatively low. However, all children in both the OSA and control groups were exposed to the same environmental conditions. Furthermore, a recent study reported that children with OSA did not experience first-night effects differently from other 2–6-yr-old children, and that respiratory parameters were not vulnerable to the presence of first-night effects [42].

Although all the children were sampled from an at-risk population, the subjects whose participation was complete, *i.e.* those who filled in and returned the screening questionnaire, participated in initial PSG evaluation and cognitive assessment, followed treatment recommendations and returned for post-operative evaluation, could differ from those who selected not to participate in one or all of the phases of the study. It is possible that this self-selection bias is somewhat alleviated by the intra-individual pre-/post-treatment comparisons, and by the fact that such biases are also applicable to the control population.

It is also possible that adult illiteracy may have played a role in the low response rates to the survey questionnaire, that difficulty with transportation and inconsistent housing may have prevented some families from participating in the initial or follow-up evaluations, and that problems with health insurance may have prevented some families from seeking the recommended treatment. Nevertheless, although these concerns are clearly worthy of consideration, it is unlikely that they contributed to the dynamic pre- and post-operative changes in sleep characteristics and cognitive function in the OSA-afflicted children. Overcoming these limitations through studies using assistance-based recruitment and clinically based outreach programmes may confirm and further extend the present findings, and delineate the benefits of such early assessment by providing more accurate estimates regarding the amelioration and extent of recovery from the cognitive consequences associated with OSA.

In summary, the present study has shown the difficulties inherent in screening for sleep-disordered breathing in a low socio-economic status population of children, and further emphasises the importance of such an approach in the context of the present findings, which demonstrate that sleep-disordered breathing is associated with substantial cognitive morbidity among these children. More importantly, treatment of sleep-disordered breathing may lead to normalisation of sleep and reversibility of the cognitive impairment in this population. These encouraging results in a population that would be highly unlikely to seek medical care for sleep-disordered breathing support the institution of a school-based screening programme at this early age in order to prevent long-lasting morbid consequences of sleep-disordered breathing.

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