Nocturnal Arterial Oxygen Saturation and Academic Performance in a Community Sample of Children

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ABSTRACT. *Objective.* **Hypoxemia, often assessed via pulse oximetry, is associated with neurocognitive deficits in children. The best way to qualify hypoxemia, or which level of hypoxemia already affects cognition, is unknown.**

Methods. **We assessed the association of pulse oximetry–derived variables that qualify hypoxemia with impaired academic performance in mathematics in a population-based cross-section of 995 primary school children who underwent overnight home recordings of motion-resistant new-generation pulse oximeter saturation (Spo_2). Impaired academic performance in mathematics was based on the last school report and defined as grade 4 to 6 on a 6-point scale (ie, approximately the lowest quintile grades).**

Results. **Of 10 variables under study, only the nadir of the Spo_2 values was significantly associated with impaired performance. Categories of this variable representing mild (ie, 91%–93% Spo_2; odds ratio: 1.65; 95% confidence interval: 1.06–2.56) and moderate hypoxemia (ie, ≤90% Spo_2; odds ratio: 2.28; 95% confidence interval: 1.30–4.01) both were associated with impaired performance in mathematics.**

Conclusions. **We suggest using the nadir of the Spo_2 values in an overnight study to qualify hypoxemia in future studies. This variable may predict neurocognitive deficits in school children. Mild hypoxemia, as yet widely considered benign, may already affect cognition in childhood.** *Pediatrics* **2005;115:e204–e209. URL: www.pediatrics.org/cgi/doi/10.1542/peds.2004-1256;** ***sleep-disordered breathing, hypoxemia, pulse oximetry, oxygen saturation, learning disorders.***

ABBREVIATIONS. Spo_2, oxygen saturation by pulse oximeter; D_4 event, desaturation by ≥4%; D_C event, desaturation cluster; SAT_{min}, nadir Spo_2; D_{92} event, desaturation to ≤92%; D_{90} event, desaturation to ≤90%; OR, odds ratio.

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Adverse impacts of chronic or intermittent hypoxemia on development, behavior, cognition, and academic performance have been reported in many well-designed and controlled studies in children with sleep-disordered breathing[1–6] or congenital heart disease.[7–11] Data for other clinical conditions that result in chronic or intermittent hypoxemia are sparse. In some studies, adverse effects have been noted at even mild levels of oxygen desaturation.[1] Application of pulse oximetry to detect chronic or intermittent hypoxemia is a valid, reliable, and frequently used method.[12] Several variables that qualify chronic and intermittent hypoxemia can be derived from pulse oximetry and reference ranges used to identify abnormal clinical conditions.[13] However, it is yet unclear which pulse oximetry–derived variable best predicts neurocognitive impairments in children and which level of oxygen desaturation is already harmful. The mean and nadir arterial oxygen saturation measured by pulse oximetry (Spo_2) have been reported and shown to have some relationship to decreased intelligence,[5] impaired attention,[5] and hyperactive behavior.[1,6]

We recently performed a study on the association between sleep-disordered breathing and impaired academic performance in primary school children.[14] As part of this study, children were examined for the presence of nocturnal chronic and intermittent hypoxemia using pulse oximetry. Only a weak association between intermittent hypoxemia and impaired academic performance in mathematics was found.[14] These results, however, were recently challenged: the inclusion of children with perhaps "abnormal" Spo_2 values (91%–95%) in our group defined as normal could have lowered associated risks, thereby underestimating the impact of nocturnal hypoxemia on cognition.[15] We thus reevaluated our data, now attempting to form a proper "normoxic" reference and to find the pulse oximetry–derived variable that best predicts impaired academic performance. Because our previous results suggested a relationship between nocturnal hypoxemia and performance in mathematics, we focused on this school subject. To investigate for an independent relationship, we also decided to assess the association between nocturnal hypoxemia and academic performance in a sample of children who were free of congenital heart disease and unlikely to experience sleep-disordered breathing.

METHODS

The recruitment strategy has been described elsewhere.[14,16] In short, 1760 third graders in 27 primary schools located within the city limits of Hannover, Germany, were approached between February 2001 and December 2001, and 1144 children finally participated. The study protocol was approved by the institutional review board, and the regional directorate of education and parents of participating children gave their informed written consent.

Questionnaire

An extended version of Gozal's sleep-disordered breathing questionnaire was used.[4,16–18] This questionnaire included questions on gender, age, parental graduation from school (4-point scale: no graduation/primary school, secondary school, high school, or college/university), and frequency of snoring (4-point scale: never, occasionally, frequently, or always). Children, who snored "never" or only "occasionally" were grouped together as nonsnorers; the remainders were categorized as habitual snorers.

Pulse Oximetry

All children underwent nocturnal home pulse oximetry. Detailed information on this method has been published elsewhere.[13,14] After data acquisition, artifact-free recording periods were identified using data analysis software (Matlab; MathSoft Inc, Cambridge, MA). This software was also used to calculate the median, 10th percentile, and 5th percentile Spo_2, as well as the number of desaturations by ≥4% (D_4 events) and desaturation clusters (D_C events[19]) within the artifact-free recording period. Recordings with <5 hours of artifact-free recording were excluded. The nadir Spo_2 (SAT_{min}) and the number of desaturations to ≤92% (D_{92} events) and to ≤90% Spo_2 (D_{90} events) were determined manually using information on signal quality, low perfusion, and pulse wave form.[13,20] The D_C events all were confirmed manually to identify artifacts.

In addition, the average distance from 100% Spo_2 and a cumulative hypoxemia score were calculated for each recording. For the cumulative hypoxemia score, the percentage of time within the artifact-free recording period with (1) Spo_2 >95%, (2) Spo_2 91% to 95%, (3) Spo_2 86% to 90%, (4) Spo_2 81% to 85%, and (5) Spo_2 ≤80% was calculated, then multiplied by 1 (Spo_2 >95%), 2 (Spo_2 91%–95%), 4 (Spo_2 86%–90%), 8 (Spo_2 81%–85%), and 16 (Spo_2 ≤80), respectively, and added up. Finally, 100 was subtracted from the resulting score so that a recording with the Spo_2 always >95% had a cumulative hypoxemia score of 0. These scores were developed to ascertain the area under the Spo_2 curve as a way to quantify hypoxemia across individuals in the context of outcomes.

To investigate the accuracy of the data analysis software, we determined the number of D_4 events manually as well as automatically in a subsample of 90 children.[13] This revealed an excellent correlation (Spearman correlation coefficient: 0.983; $P < .001$) between manual and automatic analysis. Desaturation indices, defined as events per hour of artifact-free recording, were calculated for D_4, D_{92}, D_{90}, and D_C events. A customized questionnaire covering various clinical conditions that potentially influence oximetry results was distributed on the day of the recording.[13,16] This questionnaire included the following question: "Does your child have any heart disease (eg, cardiac insufficiency)? If yes, please specify." In 1 school (34 children), test-retest reliability of pulse oximetry–derived variables was tested on 2 consecutive nights.

Academic Performance

On the basis of last term's report form (including grades on a 6-point scale: 1 for "outstanding" and 6 for "failed"), impaired academic performance in mathematics was defined as grade 4 or worse or requirement for special assistance.[14]

Statistics

All analyses were done with statistical software (Statistical Package for the Social Science, release 11.0 for Windows; SPSS, Chicago, IL). Descriptive statistics were used to summarize subject characteristics, questionnaire results, and pulse oximetry data. Differences between groups were ascertained with Pearson χ^2 test or the Mann-Whitney U test where appropriate. Correlations between pulse oximetry–derived variables obtained during 2 consecutive nights (test-retest reliability) were investigated using Spearman correlation coefficient. To quantify the associations between pulse oximetry–derived variables and impaired academic performance, we calculated odds ratios (ORs) and their 95% confidence intervals using unconditional logistic regression. Logistic models were adjusted for gender (categorical variable), age (continuous variable), maternal and paternal education (2 categorical variables), and class membership (categorical dummy variable). The last factor was found to be significantly related to both pulse oximetry–derived variables and impaired academic performance and thus met criteria for entering this variable as a potential confounder. To control for confounding by congenital heart disease and sleep-disordered breathing, we repeated analyses in nonsnorers and children without a history of heart disease. Associations between habitual snoring, a history of heart disease, and mild as well as moderate hypoxemia were investigated using Pearson χ^2 test. $P < .05$ was considered statistically significant.

RESULTS

Study Sample

A detailed description of the underlying study population and the study sample has been presented elsewhere.[14,16] In brief, of 1144 children who returned completed questionnaires, 1115 underwent oximetry recordings. Of these, 995 recordings were considered sufficient for the study purpose. Subject characteristics are given in Table 1. Among children with a history of heart disease, the following diagnoses (numbers in parentheses) were provided by parents: systolic murmur (3), ventricular septal defect (2), pulmonary artery stenosis (1), pulmonary vein stenosis (1), arrhythmia (1), cardiac insufficiency (1), and cardiac valve stenosis (1). Descriptive statistics and correlations for pulse oximetry–derived variables are presented in Table 2.

Nocturnal Hypoxemia and Impaired Academic Performance

As expected, logistic regression analyses showed negative associations (OR: <1) between baseline variables and impaired academic performance in

TABLE 1. Subject Characteristics ($N = 995$)

Characteristic	Study Sample
Gender, *n* (%)	
Boys	507 (51.0)
Girls	488 (49.0)
Age, y, mean (SD)	9.6 (0.7)
Body mass index, kg/m^2, mean (SD)	17.4 (2.9)
Low maternal education, no graduation/primary school, *n* (%)	237 (23.8)
Impaired academic performance in mathematics, *n* (%)	189 (19.0)
Habitual snoring, *n* (%)*	99 (9.9)
History of heart disease, *n* (%)	10 (1.0)

* No information on snoring available in 14 subjects.

TABLE 2. Pulse Oximetry-Derived Variables

Pulse Oximetry–Derived Variable	Descriptive Statistics (N = 995)			Test-Retest Correlations (N = 34)	
	Median	IQR	Range	Coefficient	P Value
SAT_{50}	98	98–99	93–100	0.720	<.001
SAT_{10}	97	97–98	78–99	0.720	<.001
SAT_5	97	97–98	70–99	0.514	.002
SAT_{min}	93	92–94	59–97	0.488	.003
DI_4	0.9	0.4–1.7	0.0–17.1	0.527	.001
DI_C	0.0	0.0–0.0	0.0–2.1	0.734	<.001
DI_{92}	0.0	0.0–0.1	0.0–2.6	0.707	<.001
DI_{90}	0.0	0.0–0.0	0.0–1.4	0.656	<.001
Average distance from 100% Spo_2	1.84	1.45–2.29	0.22–7.85	0.833	<.001
Cumulative hypoxemia variable	0.15	0.04–0.55	0.00–246.79	0.590	<.001

SAT_{50} indicates median Spo_2; SAT_{10}, 10th percentile Spo_2; SAT_5, 5th percentile Spo_2; DI_4, number of desaturations by ≥4% Spo_2/hour of AFRP; DI_C, number of desaturation clusters/hour of AFRP; DI92, number of desaturations to ≤92% Spo_2/hour of AFRP; DI90, number of desaturations to ≤90% Spo_2/hour of AFRP; IQR, interquartile range; AFRP, artifact-free recording period.

mathematics and positive associations (OR: >1) between desaturation/hypoxemia variables and impaired performance. The baseline SAT_{min}, however, was the only pulse oximetry–derived variable that was statistically significantly associated with impaired academic performance in mathematics (Table 3). There was a negative association between the SAT_{min} and impaired performance showing decreasing odds for impaired performance with increasing SAT_{min} values.

To transform the SAT_{min} into a categorical variable, we used the 75th percentile (94%) to delimit a reference range (94%–100% SAT_{min}) from a mildly (91%–93% SAT_{min}) and a moderately hypoxemic range (≤90% SAT_{min}). The last cutoff value (approximately the 15th percentile) was chosen because it was associated with impaired academic performance in a previous study.[14] Logistic regression analysis including this categorical variable revealed a clear dose–effect gradient and a statistically significant association between mild and moderate nocturnal hypoxemia and impaired performance in mathematics (Table 4).

Nocturnal Hypoxemia, Habitual Snoring, and Heart Disease

There were no statistically significant differences between habitual snorers and nonsnorers for any pulse oximetry–derived variable under study (Mann-Whitney U test: all $P > .05$). In addition, there was no significant difference in the prevalence of mild (habitual snorers vs nonsnorers: 44.4% vs 42.9%) and moderate hypoxemia (19.2% vs 15.3%). Children with a history of heart disease, however, were somewhat more likely to exhibit mild hypoxemia than those without (prevalence of mild and moderate hypoxemia: 80.0% vs 42.7% and 0.0% vs 15.9%; Pearson χ^2 test: $P = .053$). To test for an independent association, we excluded children with a history of heart disease and/or habitual snoring and repeated logistic regression for this subgroup (Table 5). This showed a statistically significant association between moderate but not mild hypoxemia and impaired academic performance in mathematics.

DISCUSSION

Prompted by a recent review on hypoxemia and neurobehavioral impairments in children in this journal,[15] we reevaluated data from a cross-sectional study on hypoxemia during sleep in children.[14] Although only moderately stable across 2 consecutive nights, the SAT_{min} was the only pulse oximetry variable that significantly predicted impaired academic performance in mathematics. A clear dose–effect gradient was observed, which concurs with the generally accepted hypothesis of a causal relationship

TABLE 3. Adjusted ORs for the Association Between Impaired Academic Performance and Nocturnal Hypoxemia Defined by Different Pulse Oximetry–Derived Variables (n = 995)

Pulse Oximetry–Derived Variable	Impaired Performance in Mathematics		
	OR	95% CI	P Value
SAT_{50}	0.85	0.67–1.08	.181
SAT_{10}	0.98	0.86–1.13	.821
SAT_5	0.97	0.88–1.06	.480
SAT_{min}	0.92	0.87–0.97	.004
DI_4	1.08	0.94–1.23	.267
DI_C	1.06	0.36–3.09	.921
DI_{92}	1.33	0.74–2.40	.338
DI_{90}	1.43	0.31–6.52	.644
Average distance from 100% Spo_2	1.19	0.95–1.50	.140
Cumulative hypoxemia variable	1.00	0.99–1.01	.929

ORs are adjusted for gender (categorical variable), age (continuous variable), maternal and paternal education (two categorical variables), and class membership (categorical dummy variable). CI indicates confidence interval.

TABLE 4. Prevalence of Impaired Academic Performance in Mathematics and Adjusted ORs for the association Between Impaired Academic Performance in Mathematics and Nocturnal Hypoxemia Defined by Different Ranges of SAT_{min} (n = 995)

Pulse Oximetry–Derived Variable	Definition, %	Prevalence, %	OR	95% CI	P Value
SAT_{min}	≥94	16.5	1.00	Reference	—
	91–93	20.4	1.65	1.06–2.56	.027
	≤90	24.5	2.28	1.30–4.01	.004

ORs are adjusted for gender (categorical variable), age (continuous variable), maternal and paternal education (two categorical variables), and class membership (categorical dummy variable).

TABLE 5. Adjusted ORs for the Association Between Impaired Academic Performance in Mathematics and Nocturnal Hypoxemia Defined by Different Ranges of SAT_{min} in a Sample of Children Without Habitual Snoring and Heart Disease (n = 859)

Pulse Oximetry–Derived Variable	Definition, %	OR	95% CI	P Value
SAT_{min}	≥94	1.00	Reference	—
	91–93	1.42	0.86–2.35	.172
	≤90	2.03	1.07–3.83	.029

ORs are adjusted for gender (categorical variable), age (continuous variable), maternal and paternal education (two categorical variables), and class membership (categorical dummy variable).

between hypoxemia and neurocognitive impairment.[15] In addition to moderate hypoxemia (≤90% SAT_{min}), mild hypoxemia (91%–93% SAT_{min}) was significantly associated with impaired performance. This is surprising given that this level of arterial oxygen saturation is frequent in children.[13,21] In addition, the association between SAT_{min} and impaired performance remained significant after excluding children with a history of heart disease or habitual snoring.

Several studies showed associations between neurobehavioral impairment and clinical conditions that likely lead to chronic or intermittent hypoxemia. Only a few studies, however, actually measured oxygen saturation or provided specific information on Spo_2 levels. To our knowledge, none has yet examined various pulse oximetry variables for their ability to predict neurocognitive impairment. In 2 studies, the SAT_{min} was used to qualify nocturnal hypoxemia, and associations with impaired intelligence, attention, and behavior were observed.[5,6] These and our data suggest that the SAT_{min} is an accurate predictor for neurocognitive impairment in children and may be used as a standard variable in the evaluation of children.

Little is known about mild hypoxemia and its impact on cognition in children. Although associations between neurobehavioral impairments and saturation levels of <90% Spo_2 have been reported,[1,14] the clinical significance of Spo_2 levels between 90% and 95% is unknown. The 2 studies mentioned above observed impaired outcome in children with SAT_{min} values in the lower 90s (90.7% and 90.9%),[5,6] and a recent study found associations between mean SAT_{min} values of 94.1% and neurocognitive impairments in children with primary snoring.[18] We included children with a SAT_{min} in the upper quartile in a "normoxic" reference group. This approach enabled us to detect a subtle association between mild hypoxemia (SAT_{min} 91%–93%) and impaired academic performance. However, is this finding biologically plausible? Also, why was it only the SAT_{min} that was significantly associated with impaired academic performance, not any of the other pulse oximetry–derived variables? Our study was not designed to investigate mechanisms to address these questions, and comprehensive data from other studies on the impact of mild hypoxemia on cognition are lacking.[15] We speculate, however, that a reduced SAT_{min} in a 1-night recording may reflect a "tip of the iceberg" phenomenon, ie, an increased propensity of an individual to desaturate during sleep and occasionally even further than in this 1-night study. Alternatively, mild hypoxemia could be a proxy for unstudied third variables such as sleep disruption/fragmentation, multiple arousal, or nocturnal movement or could lead per se to these pathophysiologic consequences. If this is true, then these factors may have a greater part to play in academic performance than they have been credited for.

Chronic or intermittent hypoxemia is well known to occur in children with congenital heart disease or sleep-disordered breathing and result in neurocognitive impairment. We, however, found no significant differences in the occurrence of mild and moderate hypoxemia in children with and without these conditions. Moreover, there was a strong and significant association between moderate hypoxemia (SAT_{min} ≤90%) and impaired performance in a sample of children who were unlikely to experience congenital heart disease or sleep-disordered breathing. Thus, other factors that result in hypoxemia and neurocognitive impairment likely contributed to this finding. For example, asthma is known to be associated with both hypoxemia[22,23] and neurobehavioral impairment.[24,25] More studies are needed to investigate potential causes of mild and moderate hypoxemia in otherwise healthy children.

Limitations

Some of the limitations of the present study have been discussed elsewhere.[14] In brief, because of the

cross-sectional study design, we were unable to prove a temporal sequence between nocturnal hypoxemia and impaired academic performance as 1 important aspect of causality. We cannot fully rule out that our findings might be affected by sampling bias, unreliable data collection, or incomplete adjustment for confounding factors. In addition, it cannot be fully excluded that the associations reported are chance findings. Multiple explorative significance tests involving several pulse oximetry variables were performed. Notwithstanding this concern, the association between the SAT_{min} variable and impaired performance remained significant after a Bonferroni correction, making the occurrence of a type 1 error unlikely. Sampling bias would require the overrepresentation of children with impaired academic performance exhibiting low SAT_{min} values. As parents were not aware of the exposure (chronic or intermittent hypoxemia), sampling bias was unlikely to occur. This conclusion is also supported by our comparisons for representativeness.[16]

Using motion-resistant new-generation pulse oximetry, information on signal quality and low perfusion, software-supported manual analysis, and rigorous event definitions including the pulse wave form signal, we accurately identified nighttime chronic or intermittent hypoxemia. An artifact-free recording time of >5 hours was considered sufficient for the study purpose. We, hence, might have failed to detect some hypoxic episodes during the night. This would have led to misclassification and lowered associated risks. We also measured nocturnal saturation across a time span of almost 1 year. Thus, influences related to seasonal variations (eg, colds, allergies) may have occurred. We carefully examined this potential bias but did not find a statistically significant trend (data not shown). Given that the highest prevalence of moderate hypoxemia was found in April (26.9%), one could suspect, however, a relationship between allergies and nocturnal hypoxemia. This should be an objective of future studies.

For the assessment of neurocognitive ability, we used school grades. Grades provide only a rudimentary assessment of cognitive and learning capabilities. The use of teacher ratings, however, was justified by past studies that found relationships between biological risks and similar teacher ratings.[4,17] No child was clinically evaluated for the presence of congenital heart disease; neither was sleep-disordered breathing ruled out by a standard evaluation. Hence, some children in the subsample who were suggested not to be affected by either condition may have experienced 1 or both. However, it is difficult to explain why parents should conceal a congenital heart disease or how significant sleep-disordered breathing occurs without its major symptom (ie, habitual snoring). Last, we could account for several social and school-related confounding factors (parental education and teachers' ratings). Despite this, it is possible that an unstudied variable related to impaired performance was responsible for part or all of the associations reported herein. Sleep disruption, for instance, might be the underlying cause for impaired academic performance, and nocturnal hypoxemia was only a proxy.

CONCLUSION

This study supports previous reports suggesting that mild and moderate hypoxemia lower cognitive abilities in children. The SAT_{min} was identified as a significant predictor for impaired academic performance and may be used to quantify hypoxemia in future studies. Mild hypoxemia seems to be frequent in primary school children, and more studies are needed to understand its clinical significance. Neurocognitive consequences should be considered if children are exposed to or not withdrawn from chronic or intermittent hypoxemia. Apart from congenital heart disease and sleep-disordered breathing, factors that result in chronic or intermittent hypoxemia should be identified to lower the incidence of mild cognitive impairment in children.

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