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REVIEW ARTICLE

The Effect of Chronic or Intermittent Hypoxia on Cognition in Childhood: A Review of the Evidence

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ABSTRACT. *Objective.* **A review of the evidence concerning the effect of chronic or intermittent hypoxia on cognition in childhood was performed by using both a systematic review of the literature and critical appraisal criteria of causality. Because of the significant impact of behavioral disorders such as attention-deficit/hyperactivity disorder on certain cognitive functions as well as academic achievement, the review also included articles that addressed behavioral outcomes.**

Methods. **Both direct and indirect evidence were collected. A structured Medline search was conducted from the years 1966-2000 by using the OVID interface. Both English- and non–English-language citations were included. Significant articles identified by the reviewers up to 2003 were also included. To be included as direct evidence, an article needed to be an original report in a peer-reviewed journal with data on cognitive, behavioral, or academic outcomes in children up to 14 years old, with clinical conditions likely to be associated with exposure to chronic or intermittent hypoxia. Indirect evidence from other reviews and publications in closely related fields, including experimental studies in adults, was used to help formulate conclusions. Two reviewers screened abstracts and titles. Each article included as direct evidence received a structured evaluation by 2 reviewers. Adjudication of differences was performed by a group of 2 reviewers and a research consultant. After this review, tables of evidence were constructed that were used as the basis for group discussion and consensus development. Indirect evidence assigned by topic to specific reviewers was also presented as part of this process. A formal procedure was used to rank the studies by design strength. The critical appraisal criteria for causation described in *Evidence Based Pediatrics and Child Health* (Moyer V, Elliott E, Davis R, et al, eds. London, United Kingdom: BMJ Books; 2000:46–55) were used to develop consensus on causality.**

Results. **A total of 788 literature citations were screened. For the final analysis, 55 articles met the criteria for inclusion in the direct evidence. Of these, 43 (78.2%) reported an adverse effect. Of the 37 controlled studies, 31 (83.8%) reported an adverse effect. Adverse effects were noted at every level of arterial oxygen saturation and for exposure at every age level except for premature newborns. The studies were classified into 5 clinical categories: congenital heart disease (CHD), sleep-disordered breathing (SDB), asthma, chronic ventilatory impairment, and respiratory instability in infants. Two of these categories, CHD and SDB, which accounted for 42 (76.4%) of the included articles, fulfilled the *Evidence Based Pediatrics and Child Health* criteria for causation. The indirect evidence included 8 reviews, 1 meta-analysis, and 10 original reports covering the fields of adult anoxia, animal research, SDB in adults, natural and experimental high-altitude studies, perinatal hypoxic-ischemic encephalopathy, anemia, and carbon-monoxide poisoning. The studies of high-altitude and carbon-monoxide poisoning provided evidence for causality.**

Conclusions. **Adverse impacts of chronic or intermittent hypoxia on development, behavior, and academic achievement have been reported in many well-designed and controlled studies in children with CHD and SDB as well as in a variety of experimental studies in adults. This should be taken into account in any situation that may expose children to hypoxia. Because adverse effects have been noted at even mild levels of oxygen desaturation, future research should include precisely defined data on exposure to all levels of desaturation. *Pediatrics* 2004;114:805–816; *hypoxia, cognition, development, behavior, academic achievement.***

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ABBREVIATIONS. ADHD, attention-deficit/hyperactivity disorder; SDB, sleep-disordered breathing; USPSTF, US Preventive Services Task Force; EBPCH, *Evidence Based Pediatrics and Child Health*; CHD, congenital heart disease; SaO_2, arterial oxygen saturation; CI, confidence interval.

BACKGROUND

Serious hypoxic-ischemic events are known to have an adverse impact on cognitive function.[1] Whether either chronic or intermittent subclinical hypoxia poses a similar risk has not been as well established, particularly for milder levels of oxygen desaturation. A number of recent reports in the pediatric literature have demonstrated that exposure of infants to subclinical hypoxia takes place in a variety of settings including seating devices,[2] slings,[3] airline travel,[4] and residence at high altitude.[5] Decisions about the minimum acceptable oxygen saturation

also play a role in the management of common respiratory conditions such as bronchiolitis and asthma.

Although establishing safe lower limits of oxygenation has important clinical implications, the known risk of severe hypoxic-ischemic events precludes ethical performance of a prospective, randomized, clinical trial that includes deliberate exposure of children to mild or moderate hypoxia. Therefore, to gain an understanding of this vital question, we need to rely on studies of children whose hypoxic exposure was a part of natural disease processes.

It is the purpose of this report to review the evidence concerning the effect of chronic or intermittent hypoxia on childhood cognitive outcomes including development and academic achievement and to assess the importance of factors such as intensity and age of exposure to hypoxia. Because of the significant impact of behavioral disorders such as attention-deficit/hyperactivity disorder (ADHD) on certain cognitive functions (eg, perception, recognition, and judgment) as well as on academic achievement, the review also included articles that addressed behavioral outcomes.

A systematic review of the literature directly related to the topic was performed and was used as the basis for developing consensus on causality among a group of academic pediatricians representing a variety of disciplines. In addition to the direct evidence reviewed, there exists a wide range of relevant research in related areas that provides indirect evidence of interest. This includes studies of anoxia in adults, animal research, sleep-disordered breathing (SDB) in adults, effects of actual and simulated high-altitude on cognition, perinatal hypoxic-ischemic encephalopathy, and exposure to conditions that interfere with oxygen utilization and transport. Although a comprehensive review of these topics is beyond the scope of the present effort, published reviews and research reports of indirect evidence were identified both in the course of the literature search and by our reviewers. These articles were used in the process of consensus development to provide a contextual framework that might help shed some light on the research directly related to the subject. This is particularly important, because experimental studies that will never be possible in pediatric populations do exist in some of these other fields.

METHODS

A comprehensive (1966–2000) Medline literature review was performed using the OVID interface to identify articles relating hypoxia to cognition, behavior, and school performance. Various combinations of all forms of keywords (hypoxia, cognition, memory, attention, behavior, school, IQ, intelligence, flicker, and sleep apnea) were used. In total, 788 possible literature citations were retrieved. Their abstracts and titles were screened by 2 of the reviewers for suitability for inclusion. Submissions by the participating reviewers were also accepted from other sources including personal files and examination of citations in the bibliographies of included studies. To be included in the direct evidence, an article had to be an original report in a peer-reviewed journal that provided data on the cognitive outcomes of children ≤14 years old with clinical conditions in which exposure to either chronic or intermittent hypoxia was likely. Ultimately, 55 articles[6–60] were identified for inclusion. They originated from 12 countries and included 1 Russian-language[19] and 3 German-language[10,32,52] studies.

Eight reviewers participated, including 2 general pediatricians, 2 pediatric pulmonologists, 2 neonatologists, and 2 developmental pediatricians. A native German-speaking general pediatrician assisted with the German-language articles. Each article was reviewed by a reviewer from each of 2 disciplines. Reviewers were not eligible to judge publications that they had written.

A standardized article-analysis form, which included details on clinical category, age, magnitude, and duration of exposure to hypoxia, research-design elements, and outcomes assessed, was developed and agreed on by the review group (available on request). The completed forms from these reviews were submitted to an independent agency (CareStat Inc), which entered the observations of each reviewer into a computerized database. Subsequently, a reconciliation process took place in which instances of discrepancies among reviewers were identified. An adjudication group consisting of a general pediatrician, a pediatric pulmonologist, and a research consultant (neonatologist) determined the most accurate answer for each data field by collectively examining the article and discussing the possible reasons for the identified discrepancy.

To assist the review team in analyzing the included articles, a process was implemented to rank the reports by strength of study-design elements. A published methodology[61] in which each study element was rated on a scale from 0 to 5 was used. This method included computing the average of the ratings of research-design elements by a group of epidemiology and research experts and the average of the ratings of outcome assessment elements by participating reviewers to generate a score for each element in every evaluation domain. The overall strength-of-study-design score combined the sum of the scores in each evaluation domain. Appendix 1 provides the final weights given to give to each scored element. The maximum possible score for any study, which included the highest value element for each evaluation domain, was 28.9. The validity of this method was confined to identifying the relative importance we wished to assign to the design and outcome elements of included studies. The scores were used only to provide a relative ranking of the articles based on design and outcome characteristics and were not used to formulate absolute judgments about the value of each article.

Articles then were sorted by clinical category, outcome measures, research-design elements, and amount and age of exposure to oxygen desaturation. Within each of these categories, articles were ranked by strength of study design to allow the group to take into account research-design and outcome characteristics when formulating judgments.

In addition, individual members of the group were assigned to report on the specific areas of research mentioned above as potential sources of indirect evidence, including consideration of several published reviews and summaries of important published research studies on the topics.

For articles included in the direct evidence, the US Preventive Services Task Force (USPSTF)[62] system was used to classify the quality of evidence (Table 1). To develop consensus whether the evidence demonstrated an adverse effect of hypoxia on cognition, the critical appraisal criteria for assessing harm and causation, described in *Evidence Based Pediatrics and Child Health* (EBPCH),[63] were used. This method, based substantially on Hill's criteria of causation,[64] is well suited to the question being addressed by the systematic review (Table 2). A group of reviewers, including members of each of the 4 disciplines participating in the process,

TABLE 1. Quality of Evidence Categories

I	Evidence obtained from at least 1 properly designed randomized, controlled study.
II-1	Evidence obtained from well-designed, controlled studies without randomization.
II-2	Evidence obtained from well-designed cohort or case-control studies, preferably from >1 center or research group.
II-3	Evidence obtained from multiple time series with or without intervention.
III	Opinions of respected authorities, based on clinical experience; descriptive studies and case reports; or reports of expert committees.

Source: US Preventive Services Task Force. *Guide to Clinical Preventive Services*. 2nd ed. Baltimore, MD: Williams & Wilkins; 1996.

met for a presentation that included tables of evidence based on the CareStat reports and a detailed analysis of the studies reviewed.

Summaries of the review articles and background articles concerning the relevant indirect evidence were also presented. By using a structured format based on the EBPCH criteria, the group analyzed whether each category of evidence fulfilled the criteria for association and/or causation.

RESULTS

Direct Evidence

Overall, 43 (78.2%) of the 55 articles reviewed demonstrated an adverse effect of hypoxia on cognition; 37 (67.3%) were reports of controlled studies, and of these, 31 (83.8%) showed an adverse effect. Table 3 provides a summary of the USPSTF classification of the evidence. Forty of the reports (72.7%) were USPSTF category II-3 studies or higher, of which 33 (82.5%) demonstrated an adverse effect.

For the purpose of the EBPCH analysis, the articles were classified into 5 distinct clinical categories. Two of these categories, congenital heart disease (CHD) and SDB, were determined by the group to fulfill the EPBCH criteria for association and causality and were considered a major source of evidence. There were 42 reports in these 2 categories, of which 19 included specific arterial oxygen saturation (SaO_2) data. The remaining categories (asthma, chronic ventilatory impairment, and respiratory instability in infants) were determined not to fulfill the EBPCH criteria. In general, although several of the studies in these categories were well designed, none of them included actual SaO_2 data, making interpretation of the results less certain.

The results by category are summarized in Tables 4-6. Although many of the articles examined multiple outcomes, which are summarized in the aggregate at the conclusion of the results section, these tables include only what were considered to be the major effects, noted with *P* values and confidence intervals (CIs) when available. All results are listed by design score. Articles with identical scores are listed alphabetically. The table annotation also provides some additional outcome details. For the developmental outcomes, standardized tests include the Cattell Scales, Stanford-Binet, Bayley Scales of Infant Development, Wechsler Intelligence Scales for Children (WISC and non-US variants), Wechsler Preschool and Primary Scale of Intelligence, Illinois Test of Psycholinguistic Abilities, and Halstead Battery. For the behavioral outcomes, standardized tests included the Continuous Performance and Auditory Continuous Performance Test. Clinical assessment questionnaires included the Conners' Scales, Child Behavior Checklist, and Developmental Behavior Checklist. For academic outcomes, the Wide Range Achievement Test was considered a standardized test.

TABLE 2. Critical Appraisal Criteria

Association
Comparison groups clearly defined
Exposure and outcome consistently and independently measured
Extent of follow-up appropriate
Evidence of confounding addressed
Likelihood of chance excluded
Causation
Temporal relationship
Biologic plausibility
Consistency of relationship
Dose response
Strength/precision of association
Cessation effects

Source: Moyer V, Elliott E, Davis R, et al, eds. *Evidence Based Pediatrics and Child Health*. London, United Kingdom: BMJ Books; 2000.

TABLE 3. Summary of Quality of Evidence

Study Type	USFSTF* Category	Category Total	Effect Shown, *n*
Quasiexperimental	II-1	1	1
Prospective cohort	II-2	7	5
Historical cohort	II-2	23	19
Case control	II-2	4	4
Multiple time series	II-3	5	4
Cross-sectional	III	5	4
Case series	III	8	5
Case report	III	2	1
		55	43

* Source: US Preventive Services Task Force. *Guide to Clinical Preventive Services*. 2nd ed. Baltimore, MD: Williams & Wilkins; 1996.

The major effects reported in the CHD studies are summarized in Table 4. An adverse effect on cognition was shown in 14 of the 17 studies (82.3%) with highly significant *P* values; 2 were rated as unclear and 1 showed no effect. Three of these reports[9,12,17] included specific differences in mean IQ that ranged from 8.3 to 9.3 points lower in full-scale IQ in cyanotic, as compared with acyanotic children. All the studies had controls, and 16 of the 17 studies (94.1%) were judged to have used the highest category of assessment methods. Eight studies (47.1%) included specific SaO_2 data.

The major effects reported in the SDB articles are summarized in Table 5. An adverse effect was shown in 23 of the 25 articles (92.0%), including 1 report[24] in which mean IQ was 12 points lower in children with snoring, as compared with controls. The snoring children in this study also had lower nadir SaO_2 levels (90.7%) than the controls (95.6%). Two studies were rated as unclear. Two sets of studies[33–35,37] included the same population at different points in time. Thirteen (52.0%) were controlled studies. Three of the articles exclusively involved children with genetic syndromes.[36,39,46] Eight of the reports (32%) were judged to have used the highest category assessment methods. Eleven (44.0%) included specific SaO_2 data.

The major effects reported in the articles that did not fulfill the EBPHC criteria are summarized in Table 6. These categories had fewer articles per category. Six of the 13 articles (46.2%) reported adverse effects on cognition, 4 were rated as unclear, and 3 showed no effect. Seven (53.8%) were controlled studies, and all used the highest category assessment methods. None of these articles had specific SaO_2 data.

SaO_2 stratified data were also reviewed when available. Because studies used a variety of methods to define hypoxia, including mean SaO_2, nadir SaO_2,

TABLE 4. Major Effects: CHD

Study			Major Effects					
Design Score	Authors	Design	Development	Behavior	Other	*P*	CI	*N*
19.4	Feldt et al[6]	Prospective cohort	Decreased IQ*			<.01	—	78
19.4	Linde et al[7]	Prospective cohort		Improved attention postop†		<.05	—	319
18.1	Aisenberg et al[8]	Historical cohort	Delayed motor development*			<.02	—	173
18.1	Aram et al[9]	Historical cohort	Decreased IQ*			0.006	—	82
18.1	Czerwenka-Wenkstetten et al[10]	Historical cohort	Decreased intelligence*			—	—	144
18.1	Kramer et al[11]	Historical cohort	Unclear*			.000004	—	217
18.1	Linde et al[12]	Historical cohort	Decreased IQ*			<.05	—	319
18.1	Newberger[13]	Historical cohort	Decreased IQ*			<.01	—	38
18.1	O'Dougherty et al[14]	Historical cohort		Impaired attention*		<.01	—	78
18.1	Silbert et al[15]	Historical cohort	Decreased IQ*			$.01 < P < .02$	—	46
18.1	Stieh et al[16]	Historical cohort	Delayed motor development†			<.03	—	102
18.1	Wright and Nolan[17]	Historical cohort	Decreased IQ*			.01	(2.32–17.72)‡	65
17.2	O'Dougherty et al[18]	Historical cohort		Impaired attention*		<.00001	—	107
16.4	Kremenva[19]	Multiple time series	Unclear			—	—	59
13.4	Aisenberg et al[20]	Historical cohort			No effect (auditory reaction time)	NS	—	239
13.4	Aisenberg et al[21]	Historical cohort			Impaired visual function (critical flicker frequency)	—	—	278
13.4	Rosenthal[22]	Historical cohort			Impaired visual function (visual simple reaction time)	<.05	—	65

— indicates that the information was not available; NS, not significant.
* Standardized psychometric testing.
† Research scale.
‡ For mean difference in Wechsler Intelligence Scales for Children IQ.

TABLE 5. Major Effects: SDB

Study			Major Effects						
Design Score	Authors	Design	Development	Behavior	Academic	Other	*P*	CI	*N*
18.7	Gozal[23]	Quasiexperimental			Improved grades after adenotonsillectomy		<.001	—	54
18.1	Blunden et al[24]	Historical cohort	Lower IQ*	Impaired attention*			<.0005†	—	32
18.1	Rhodes et al[25]	Historical cohort	Impaired learning and vocabulary*				<.05	—	14
17.8	Ali et al[26]	Multiple time series		Impaired attention‡			.003	—	33
17.8	O'Brien et al[27]	Case control		ADHD symptoms‡			<.00001	(1.8 < OR < 2.4)	110
16.8	Gozal and Pope[28]	Case control			Lower school rank		<.00001	(1.88 < OR < 4.15)	1588
16.4	Stradling et al[29]	Multiple time series		ADHD symptoms§			<.001	—	92
16.4	Weissbluth et al[30]	Case control		ADHD symptoms§	Academic problems§		<.05	—	186
16.3	Chervin et al[31]	Case control		ADHD symptoms§			.01	—	143
16.3	Paditz et al[32]	Multiple time series		ADHD symptoms§			.043	—	46
16.1	Harvey et al[33]	Prospective cohort				Symptoms (including behavior) associated with OSA§	<.05	—	39
15.8	Harvey et al[34]	Historical cohort	Parental developmental concerns§				.008	—	104
15.7	Ali et al[35]	Cross-sectional		Hyperactivity§			<.0001	(1.38 < RR < 2.18)	132
15.7	Richadale et al[36]	Historical cohort		Behavioral disturbance‡			.05		58
13.7	Ali et al[37]	Prospective cohort		Reported hyperactivity			<.0001	(1.6 < RR < 4.7)	507
13.4	Brouillette et al[38]	Case series				Neurologic dysfunction	—	—	22
13.4	Hecht et al[39]	Case series	Lower Mental Development Index*				<.05	—	13
13	Goldstein et al[40]	Multiple time series		Behavioral problems‡			<.001	—	36
12.5	Ferreira et al[41]	Cross-sectional		Behavioral disturbance§			.03	—	976
12.4	Chervin et al[42]	Cross-sectional		ADHD symptoms‡			<.01	(1.4 < OR < 3.6)	866
12.4	Owens et al[43]			Unclear‡			<.001	—	152
11.1	Guilleminault et al[44]	Case series		Unclear		Unclear	—	—	8
11.1	Guillemenault[45]	Case series		Reported hyperactivity			—	—	50
11	Rains[46]	Case series		Improved attention post-CPAP§			—	—	4
10.3	Martin and Lefebvre[47]	Case report		Psychosis			—	—	—

— indicates that the information was not available; RR, relative risk; OR, odds ratio; NS, not significant; OSA, obstructive sleep apnea; CPAP, continuous positive airway pressure.
* Standardized psychometric testing.
† For mean difference in Auditory Continuous Performance Test (<.01 for Wechsler Preschool and Primary Scale of Intelligence).
‡ Clinical assessment questionnaire.
§ Research questionnaire.

TABLE 6. Major Effects: Categories Not Fulfilling EBPCH Criteria

Study			Major Effects						
Category	Design Score	Authors	Design	Development	Behavior	Academic	Other	*P*	*N*
Asthma	18.1	Dunleavey and Baade[48]	Historical cohort	Impaired neuropsychological tests*				<.01	40
	17.2	Reitveld and Colland[49]	Historical cohort			No effect†		NS†	50
	14.8	Bender et al[50]	Cross-sectional		Behavioral disturbance‡			.005	67
	13.4	Isbister and Mayer[51]	Case series	Unclear				—	5
	13.0	Spillman[52]	Case series		Various behavior problems			—	12
Chronic ventilatory impairment	13.4	Herman et al[53]	Case series	Unclear*				—	55
Respiratory instability in infants	21.7	Kahn et al[54]	Prospective cohort	No effect*				NS	52
	21.7	Black et al[55]	Prospective cohort	Impaired development*				<.00001	122
	20.7	Koons[56]	Prospective cohort	No effect*				NS	107
	20.4	Deykin et al[57]	Historical cohort				Neurodevelopmental abnormalities	<.05	38
	20.4	Korobkin and Guilleminault[58]	Historical cohort	Developmental delays				—	69
	14.8	Baroni[59]	Historical cohort		Unclear*			.000	81
	10.9	Chang and Meerstadt[60]	Case report	Unclear				—	1

Source: Moyer V, Elliott E, Davis R, et al, eds. *Evidence Based Pediatrics and Child Health*. London, United Kingdom: BMJ Books; 2000. — indicates that the information was not available; NS, not significant.

* Standardized psychometric testing.

† $P = .033$ before Bonferroni correction.

‡ Clinical assessment questionnaire.

ranges, and thresholds to review effects noted at specific SaO_2 levels, it was necessary to establish guidelines for inclusion at a given level. It was decided that the mean SaO_2, when provided, was the most reliable indicator of exposure level. To avoid overstatement of the effect of milder levels of exposure when mean SaO_2 was not provided, the lower end of the range was used. Definitional thresholds were only included if they encompassed a single SaO_2 stratum. Using this method of classification, studies that showed adverse cognitive effects were noted for all SaO_2 strata (Table 7).

Age-specific data were reviewed for those articles in which a distinct age group of exposure could be identified. These results are summarized in Table 8. With the exception of the preterm infant, adverse effects were noted for exposure in every age group from the term newborn through age 14.

In addition to the major effects reported in Tables 4–8 many of the articles included reports of other effects observed. In the aggregate analysis, 71 different adverse effects were reported in the 55 articles. Of the 35 articles that looked for a developmental outcome, 21 (60.0%) reported an adverse outcome, as did 26 of the 36 articles (72.2%) that looked for a behavioral outcome; adverse outcomes were also present in 10 of the 14 articles (71.4%) that looked for an academic outcome and 14 of the 20 articles (70.0%) that measured other outcomes.

Indirect Evidence

The indirect evidence included a range of articles in related areas of interest. There was 1 review of anoxia in adults[65] that documented adverse neuropsychological and neuropathological outcomes, 1 review[66] on the adverse effects of hypoxia on learning and behavior in animals, and 1 review of the detrimental cognitive effects of SDB in adults.[67]

A review of altitude studies in adults,[68] which was included in the indirect evidence because of the well-established association between oxygen desaturation and high altitude,[69] summarized reports of adverse impacts on cognition, memory, mood, and behavior in a variety of natural situations as well as experimental exposures to hypoxia in altitude chambers. This review documented that studies have shown changes in memory and cognition at altitudes of 6000 to 8000 ft (corresponding to oxygen saturations in the low 90% range), the effects of which may persist for up to 1 year and may be dose-dependent.

Literature on outcomes subsequent to perinatal hypoxic-ischemic encephalopathy was included in the indirect rather than the direct evidence section because of the substantial confounding effects of concurrent ischemia.[70] There were 3 review articles on the association between hypoxic-ischemic encephalopathy and adverse cognitive and behavioral effects,[71–73] 2 studies on the negative impacts of acidosis and hypoxemia on development,[74,75] and 5 articles reporting an association between perinatal hypoxic events and schizophrenia, including a meta-analysis of 11 studies,[76] 2 prospective cohort studies,[77,78] and 2 case-control studies.[79,80]

Other articles examined the effects of problems

TABLE 7. Major Effects by SaO_2 Level

SaO_2	Study Authors	Category	SaO_2, %	Inclusion Criteria	Other SaO_2 Information (range)	Major Effects		
						Development	Behavior	Other
<80%	Aisenberg et al[8]	CHD	77.3	Mean	(48–89)	Delayed motor development		
	O'Dougherty et al[18]	CHD	66.1 (9.9)	Mean (SD)			Impaired attention*	
	Guillemenault et al[45]	SDB	<60	Definition			Reported hyperactivity	
	Rains[46]	SDB	59	Low range	(59–81)		Improved attention post CPAP†	
80–84%	Silbert et al[15]	CHD	82	Mean	(72–92)	Decreased IQ*		
	Wright and Nolan[17]	CHD	84 (9.4)	Mean (SD)		Decreased IQ*		
	Aisenberg et al[20]	CHD	81 (7.2)	Mean (SD)	(55–89)			No effect (auditory reaction time)
85–93%	Blunden et al[24]	SDB	90.7 (1.8)	Nadir (SD)	>4% drop	Lower IQ*	Impaired attention*	
	O'Brien et al[27]	SDB	90.9 (5.8)	Nadir (SD)	>4% drop		ADHD symptoms‡	
	Rosenthal[22]	CHD	85	Stratified range	(85–89)			Impaired simple visual reaction time
>94%	Stradling et al[29]	SDB	95	Mean	(86–97) >4% drop		ADHD symptoms†	

CPAP indicates continuous positive airway pressure.
* Standardized psychometric testing.
† Research questionnaire.
‡ Clinical assessment questionnaire.

TABLE 8. Major Effects by Age

Age	Study: Authors	Category*	Major Effects: Development	Behavior	Academic
Preterm	Koons et al[56]	RI	No effect†		
Term	Black et al[55]	RI	Impaired development†		
1–23 mo	Kahn et al[54]	RI	No effect†		
	Korobkin and Guillemanault[58]	RI	Developmental delays		
	Linde et al[12]	CHD	Decreased IQ†		
2–5 y	Linde et al[12]	CHD	Decreased IQ†		
	Ali et al[35]	SDB	Hyperactivity‡		
6–14 y	Gozal[23]	SDB			Improved grades after adenotonsillectomy
	Dunleavey and Baade[48]	A	Impaired neuropsychological tests†		
	Linde et al[12]	CHD	Decreased IQ†		
	Rhodes et al[25]	SDB	Impaired learning and vocabulary†		
	Ali et al et al[26]	SDB		Impaired attention§	
	Reitveldt and Colland[49]	A			No effect‖
	Bender et al[50]	A		Behavioral disturbances§	
	Ferreira et al[41]	SDB		Behavioral disturbance‡	
	Martin and Lefebvre[47]	SDB		Psychosis	

* Categories: RI (respiratory instability in infants), CHD, SDB, and A (asthma).
† Standardized psychometric testing.
‡ Research questionnaire.
§ Clinical assessment questionnaire.
‖ $P = .033$ before Bonferroni correction.

with oxygen utilization and transport on cognition, including 1 review[81] and 1 prospective cohort study[82] of the impact of iron-deficiency anemia on cognition and several reports of cognitive impairment in pediatric[83] and adult[84] survivors of carbon-monoxide poisoning. A double-blind, randomized, controlled study comparing cognitive outcomes after hyperbaric versus normobaric treatment of carbon-monoxide poisoning[85] was also included. This experimental study showed significantly fewer ($P = .007$) cognitive sequelae in the hyperbaric treatment group.

The review group concluded that, although all categories of the indirect evidence were biologically plausible and consistent with the possibility of an adverse effect from hypoxia, the altitude studies and the carbon-monoxide poisoning literature also provided evidence of both association and causality.

DISCUSSION

The purpose of this review was to determine if there is evidence in the literature suggesting that exposure to chronic or intermittent hypoxia imposes adverse cognitive effects in children. For 2 areas of direct pediatric evidence, CHD and SDB, well-designed studies have identified adverse effects on development, behavior, and academic achievement. In addition, studies in healthy adults have convincingly demonstrated evidence for adverse effects resulting from exposure to hypoxia in both natural and simulated high altitudes and in cases of carbon-monoxide poisoning. The areas of evidence that the group identified as not fulfilling the EBPCH criteria were all biologically plausible and largely consistent with the same conclusion. The fact that they did not fulfill the EBPCH criteria, however, does not preclude the possibility that more rigorous studies might have provided evidence that met the criteria of causality in those areas as well. In fact, given the consistency of effects noted in CHD and SDB, there is a clear need for more substantial research in those other categories of potential exposure to hypoxia.

As a group, the studies of CHD and SBD fulfilled the criteria of association. The issue of the potential confounding of natural causes was well addressed in the studies of CHD in which all 14 of the studies that were determined to demonstrate adverse outcomes used comparable noncyanotic control groups.[6–10,12–18,21,22] Confounding causes in the SDB group was also reasonably accounted for. Three studies[24,29,35] documented the association of snoring, O_2 desaturation, and ADHD symptoms, and the 1997 Chervin et al[31] study showed that snoring, independent of sleepiness, was associated with ADHD symptoms. Additional evidence of the importance of hypoxemia as a cause of cognitive impairment in patients with SDB was found in both a pediatric[32] and an adult study.[86]

Regarding the criteria of causation, the studies of CHD and SDB clearly demonstrated a temporal relationship and biological plausibility. There was also great consistency of effect in these groups of studies. Only 4 studies were felt to have unclear results because of a lack of clarity in either classification[11,43] or ascertainment.[19,44] The 1 study that did not demon-

strate any adverse effect[20] measured the impact of cyanotic heart disease specifically on auditory reaction time. Absence of this effect, while interesting, does not impact the validity of the results in the other studies in the group. A dose-effect association was noted in several reports.[13,14,22,42] The *P* values and available CIs were supportive of the strength and precision of the relationship (Tables 4 and 5). Cessation effects were noted in 8 reports.[7,23,26,29,32,40,46,47]

The review of studies of hypoxic exposure at high altitudes,[68] as well as the double-blind, randomized, controlled study of hyperbaric oxygen treatment for carbon-monoxide poisoning,[85] clearly showed adverse effects of even brief exposure to hypoxia on cognition in adults. Given the strong and consistent effects noted in the pediatric CHD and SBD studies, those results should lead to caution in assuming that healthy infants and children would be immune to adverse effects of similar exposure. Several studies have demonstrated that oxygen desaturation occurs in a variety of infant-positioning devices including car safety seats[2,87,88] and slings.[3] A recent commentary in *Pediatrics*[89] advocated limiting the use of car safety seats to their purpose of infant transport. This review supports that conclusion. In addition, manufacturers of all infant-positioning devices should take into account the physiologic impact of the design of these products.

An important aspect of the current review was the tabulation of effects by stratified SaO_2 level. There are 3 published reviews of the effects of SDB on cognition in children,[90–92] including a technical report by the Subcommittee on Obstructive Sleep Apnea Syndrome of the American Academy of Pediatrics Section on Pediatric Pulmonology.[92] Although each of these reviews supports the adverse effects of SDB on cognition, they did not include stratified SaO_2 levels in their analyses. As shown in Table 7, adverse effects have been demonstrated even at milder levels of desaturation, including lower IQ[24] and ADHD symptoms.[24,27,29] These results show the importance of providing long-term follow-up including behavioral outcomes when studying the potential effects of hypoxia. Future research in this area should always include clearly defined information on the amount of time spent at all SaO_2 levels that are below the published norms (which range from 93 to 100% depending on age),[93–96] including milder levels of desaturation that do not demonstrate obvious acute morbid effects.

The review also considered the effects of age of exposure on outcome (Table 8) and noted adverse outcomes at every age category except for preterm infants. It is important to recognize, however, that the 1 study of exclusively preterm infants in the review[56] was performed on apneic infants on home monitors and did not include specific SaO_2 data. Because another study in the review showed better outcomes in monitored versus unmonitored infants,[55] it is possible that the monitored infants did not experience significant time periods of desaturation. It is possible also that there may be some protective factor in premature infants (eg, enhanced anaerobic metabolism). This is an area in need of additional research.

Another interesting finding of the review was the documented vulnerability of children with a variety of genetic syndromes[36,39,46] to the adverse effects of hypoxia. Because many of these children do not have the inherent cognitive strengths of healthy children, any adverse impact of hypoxia may have a more profound impact on their quality of life. This is an area that warrants additional study.

Subsequent to the completion of the formal review process, there have been several recently published studies of interest. Although limited by the fact that they were not subjected to the selection process and critical appraisal criteria used in the review, they are germane to the topic and worthy of comment. There were 4 new reports in the field of SDB.[97–100] Two studies confirmed the findings of neuropsychological and behavioral effects associated with SBD,[97,98] including evidence of an association between verbal IQ and nadir SaO_2.[98] A third study,[99] which showed only a weak association between oxygen desaturation and poor academic performance (mathematics), was flawed by including children with abnormal saturations (91–95%) in the group defined as normal, making it difficult to draw conclusions from this report. The fourth study,[100] a prospective cohort of 239 children aged 6 to 11 years old, documented the contribution of hypoxemia as an important predictive variable for learning problems ($P < .02$) in children with SDB, which confirms the observations of Chervin et al,[31] Paditz et al,[32] and Findley et al[86] concerning the observation that hypoxemia, in addition to sleep disruption, is an important contributing factor to the adverse outcomes associated with SDB.

There was also a recently published experimental study of the impact of differing therapeutic oxygen saturation targets in extremely preterm infants.[101] This study did not show a difference in development at a corrected age of 12 months between infants managed at low (91–94%) versus high (95–98%) saturation targets. Although interesting from the perspective of neonatology management, the study does not shed light on the current question for several reasons. The most significant limitation is that half of the SaO_2 range in the low-saturation group was normal for age (93–94%).[93] In addition, development at 12 months old may not correlate with later cognitive and academic achievement, and the observation that nearly one fourth of both groups had developmental abnormalities suggests that the major effect on development was related to extreme prematurity and its associated complications. However, as mentioned above, prematurity may confer some protection against the adverse impacts of hypoxia, and if confirmed at clearly hypoxic levels and with long-term follow-up, these results would be significant.

As a final point, certain limitations of the review should be mentioned. Because the studies in the systematic review were not homogeneous enough to warrant meta-analysis, apart from some of the examples of mean IQ comparisons noted in the results, overall magnitude of effect cannot be inferred. In

addition, other than the mention of the Bonferonni correction in 1 report,[49] the issues of power and magnitude of expected effect are not addressed in the negative studies.

The possibility of publication bias, in which negative results are less likely to be accepted for publication,[102] also needs to be considered. In the present review, however, a sincere effort was made to limit publication bias throughout the process, including the translation of foreign-language articles as well as inclusion of studies identified by the reviewers apart from the systematic search. We therefore feel that the likelihood of missing a significant number of peer-reviewed published studies that did not demonstrate an adverse effect is minimal. Although we did, by design, exclude non–peer-reviewed sources in which negative results might have been published, because these reports are not well accepted we feel that this limitation would not have modified our conclusions substantively.

CONCLUSIONS

Adverse impacts on development, academic achievement, and behavior have been clearly documented in many well-designed controlled pediatric studies of CHD and SDB and in a variety of experimental studies of otherwise healthy adults. Some of the adverse effects were noted in reports with oxygen saturations just below the range of normal for age. This information should be taken into account when managing clinical conditions and designing devices that may expose infants or children to any level of chronic or intermittent hypoxia, with the goal of minimizing potential risk whenever possible. Such risks should also be balanced with the potential risks of oxygen therapy.[103] Because the precise minimal exposure that may result in adverse effects is currently unknown, future research in this area should provide specific information on SaO_2 levels observed as well as data on the duration of exposure to mild levels of oxygen desaturation.

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APPENDIX 1. Design Score Values

Items	Score
1. Design	
Case report	0.5
Case series	1.3
Cross-sectional	2.7
Ecologic	2.7
Case control	3.3
Prospective cohort	4.0
Historical cohort	2.7
Multiple time series	3.3
Quasiexperimental	3.7
Experimental	5.0
2. Sample Selection	
Random sample selection	5.0
Systematic sample selection	3.0
Convenience sample selection	1.7
3. Controlled Elements	
Controlled	
Yes	4.8
No	1.5
4. Randomized Process	
Randomized intervention	
Yes	4.8
No	2.0
5. Blinded Assessment	
Blinded	
Yes	4.5
No	2.2
6. Outcome	
Development (standardized test)	4.7
Development (report)	2.4
Behavioral (observed)	3.8
Behavioral (report)	2.3
Academic achievement (assessed)	4.3
Academic achievement (reported)	2.4

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The Effect of Chronic or Intermittent Hypoxia on Cognition in Childhood: A Review of the Evidence

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