

# Modern MEDICINE PEDIATRIC DIGEST

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## Sleep Duration and Risk for Overweight in Preschoolers



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*Infants and toddlers who sleep fewer than 12 hours per day have higher risk for being overweight at age 3 years than children who sleep 12 hours or more.*

Several studies in adults have linked sleep deprivation with weight gain, obesity, and coronary artery disease. Lack of sleep causes decreases in the hormone leptin and increases in the hormone ghrelin, and this combination might cause increased hunger beyond a person's energy expenditure. To examine whether sleep duration in infancy and early childhood correlates with adiposity at age 3 years, researchers conducted a longitudinal study in 915 infants (defined as ages 6 months to 2 years).

Mothers reported their children's total daily sleep duration (naps and nighttime sleep) at ages 6 months, 1 year, and 2 years and hours of active play and television watching at 2 years. Children's weight, height, and skinfold thickness were measured at ages 6 months and 3 years. Overall, only 9% of children were overweight (BMI >95th percentile for age and sex) at age 3 years. However, the proportion of children who were overweight at age 3 years was significantly higher among those who slept fewer than 12 hours per day on average than among those who slept 12 or more hours (12% vs. 7%). Average sleep duration of fewer than 12 hours per day was significantly associated with higher BMI z scores and higher subscapular and triceps skinfold thicknesses (after adjustment for maternal education, income, prepregnancy BMI, marital status, and prenatal smoking; breastfeeding duration; and child's ethnicity, birth weight, weight-for-length z score at 6 months, average daily television time, and average daily active time). Further, children who slept fewer than 12 hours per day were more than twice as likely to be overweight at age 3 years as those who slept longer. Children who slept fewer than 12 hours and spent more than 2 hours per day watching television were nearly six times more likely to be overweight at age 3 years than those who slept 12 hours or more and watched fewer than 2 hours of television per day.

**Comment:** Many variables affect sleep duration in infants, including hours at day care, parents wanting to spend time with their children, co-sleeping, and frequent night waking. Parents often state: "My baby is like me and doesn't need much sleep" or "If I put him to bed too early, I will never see him." These results can help support discussions with parents about the detrimental effects of inadequate sleep on children's health.

— Robin Drucker, MD

### **CITATION(S):**

Taveras EM et al. Short sleep duration in infancy and risk of childhood overweight. *Arch Pediatr Adolesc Med* 2008 Apr; 162:305.

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## Does Supplemental Oxygen Keep Infants with Bronchiolitis in the Hospital?

*Oxygen supplementation determines length of stay in hospitalized infants with bronchiolitis when the oxygen threshold is <94% SpO<sub>2</sub>.*

Although the AAP Clinical Practice Guideline for management of bronchiolitis does not recommend routine supplemental oxygen for infants and young children with bronchiolitis and pulse oxygen saturation (SpO<sub>2</sub>) values 90%, decisions to start and stop supplemental oxygen vary widely in practice. To examine the effect of supplemental oxygen on length of stay (LOS), Scottish investigators conducted a retrospective case study of 102 randomly selected infants (mean age, 24 weeks) who were admitted to a medical ward with acute viral bronchiolitis. Infants received standardized care with continuous SpO<sub>2</sub> monitoring and supplemental oxygen at SpO<sub>2</sub> of <94% in room air and did not receive any unproven treatments (bronchodilators, corticosteroids, antibiotics). Respiratory syncytial virus infection was documented in 76%. Infants admitted to the pediatric ICU (PICU) were excluded.

Overall, 22% of infants required oxygen at admission, 70% required supplemental oxygen (mean duration, 56 hours) during hospitalization, and 82% had feeding problems (mean duration, 27 hours) requiring nasogastric tube feedings (none required intravenous fluid). SpO<sub>2</sub> levels at admission (mean, 94%) and at 6 hours did not correlate significantly with LOS. Duration of oxygen supplementation strongly correlated with LOS. The primary determinant of LOS was use of oxygen supplementation in 57% of infants (mean LOS, 94 hours) and feeding problems in 26% (mean LOS, 30 hours). The average time from resolution of feeding problems to resolution of oxygen requirement was 66 hours. No infant required PICU admission.

**Comment:** Although this study is limited by its observational retrospective design, it is strengthened by the standardized treatment of patients. The findings suggest that use of oxygen supplementation usually determines LOS for infants with bronchiolitis when the supplementation threshold is <94% SpO<sub>2</sub>. However, the approach to supplementation used in this study differs from the AAP guideline for management of bronchiolitis: The AAP recommends intermittent instead of continuous SpO<sub>2</sub> measurements and an oxygen supplementation threshold of <90% SpO<sub>2</sub> instead of <94% SpO<sub>2</sub>. A similar study that adheres to the AAP guideline might find that supplemental oxygen treatment decreases LOS without adversely affecting patient outcomes.

— Cornelius W. Van Niel, MD

### CITATION(S):

*Unger S and Cunningham S. Effect of oxygen supplementation on length of stay for infants hospitalized with acute viral bronchiolitis. Pediatrics 2008 Mar; 121:470.*



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#### IMPORTANT NOTICE:

The World Health Organisation (WHO) has recommended that pregnant women and new mothers be informed of the benefits and superiority of breastfeeding - in particular the fact that it provides the best nutrition and protection from illness for babies. The Global Strategy for Infant and Young Child Feeding adopted by the 2002 World Health Assembly states that "as a global public health recommendation, infants should be exclusively breastfed for the first six months of life to achieve optimal growth, development and health." Mothers should be given guidance on the preparation for, and maintenance of, lactation, with special emphasis on the importance of a well-balanced diet both during pregnancy and after delivery. Unnecessary introduction of partial bottle-feeding or other foods and drinks should be discouraged since it will have a negative effect on breastfeeding. Similarly, mothers should be warned of the difficulty of reversing a decision not to breastfeed. Before advising a mother to use an infant formula, she should be advised of the social and financial implications of her decision; for example, if a baby is exclusively bottle-fed, more than one can (400g) per week will be needed, so the family circumstances and costs should be kept in mind. Mothers should be reminded that breast milk is not only the best, but also the most economical food for babies. If a decision to use an infant formula is taken, it is important to give instructions on correct preparation methods, emphasising that un-boiled water, unsterilised bottles or incorrect dilution can all lead to illness.

\* See: International Code of Marketing of Breast Milk Substitutes, adopted by the World Health Assembly in Resolution WHA 34.22, May 1981.

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## Chronic Fatigue Syndrome Might Occur Before Adolescence

*This report suggests that CFS can affect children as young as age 2 years and that young children can be as severely affected as older children.*

Chronic fatigue syndrome (CFS) is a disabling condition at any age, but some studies exclude children younger than 12 years. To describe CFS in younger children, investigators in the U.K. identified 178 children (age, <18 years) who were diagnosed with CFS from 2004 to 2007, based on the Royal College of Paediatrics and Child Health's definition of "generalized fatigue persisting after routine tests and investigations have failed to identify an obvious underlying cause."

At the time of assessment, 32 children (22 girls) were younger than 12 years (3 were younger than 5 years, and the youngest was age 2 years). Standardized inventories of fatigue, disability, anxiety, pain, and school absence showed that children younger than 12 years had the same number of symptoms and were as severely affected in all domains as children in the cohort who were 12 years or older. Twenty-four (of 26) children younger than 12 years satisfied the stricter CDC diagnostic criteria for CFS: new (not lifelong), unexplained (after clinical evaluation), persistent or relapsing fatigue unrelieved by rest and resulting in reduction of activities, plus at least four of the following symptoms — short-term memory impairment, sore throat, tender cervical or axillary lymph nodes, muscle pain, multiple arthralgias, headaches, unrefreshing sleep, and postexertional malaise lasting 24 hours. On average, children younger than 12 years attended school only 43% of the time.

**Comment:** The degree of disability and frustration caused by CFS is hard to imagine until one is confronted with a patient with the condition. This report suggests that CFS can start in children as young as 2 years and that young children can be as severely affected as older children. Considering the challenge in diagnosis and treatment of CFS even in adolescents, when CFS is suspected in a young patient, I would make every effort to identify a clinician or specialty center with experience in pediatric CFS. In some referral centers, a rheumatologist, an infectious diseases specialist, a developmental-behavioral pediatrician, an adolescent medicine specialist, or a child psychiatrist is a useful initial contact.

— F. Bruder Stapleton, MD

### CITATION(S):

Davies S and Crawley E. Chronic fatigue syndrome in children aged 11 years old and younger. *Arch Dis Child* 2008 May; 93:419.

## Autism Screening Is Important in Children Who Were Extremely Premature at Birth

*Toddlers who were extremely premature at birth had a high prevalence of positive screening tests for autism as toddlers.*

Population-based studies have identified prematurity and low birth weight as risk factors for later development of autism spectrum disorders. To examine this association, investigators in Boston prospectively followed a cohort of 91 extremely premature infants (gestational age, 23–30 weeks) to age 2 years. At a mean corrected age of 22 months, infants were evaluated using the Modified Checklist for Autism in Toddlers (M-CHAT), the Child Behavior Checklist (CBCL), and the Vineland Adaptive Behavior Scale (VABS). Prenatal, birth, and neonatal ICU clinical data were collected, and brain MRI was performed during initial hospitalizations.

Overall, 25% of children had positive screening results on the M-CHAT. Independent risk factors for a positive screen were lower birth weight and gestational age, male sex, evidence of chorioamnionitis, and greater illness severity at birth. Abnormal MRI findings (particularly cerebellar hemorrhage) and acute maternal intra- or antepartum hemorrhage were significantly associated with positive screening tests. Abnormal M-CHAT scores were highly correlated with internalizing behavioral problems on the CBCL and with communication and socialization deficits on the VABS.

**Comment:** The authors note the important fact that an abnormal M-CHAT result is only a positive screening test and that diagnostic testing for autism was not conducted in these children. In addition, the results of the M-CHAT when used as a screening test in this special population of premature children might differ from results in the general population. A high prevalence of developmental delays in this cohort could have contributed to the high prevalence of positive autism screening tests. The authors note, however, that positive M-CHAT screening results did not correlate with functional motor deficits on the VABS. Overall prevalence of autism spectrum disorders is now reported as high as 1 in 150 children; the recently published AAP statement on autism recommends use of the M-CHAT or other suitable screening tests in all children at ages 18 or 24 months. Despite the weaknesses of this study, autism screening for survivors of extreme prematurity and formal diagnostic testing in those with positive screening tests seem prudent.

— Cornelius W. Van Niel, MD

**CITATION(S):**

*Limperopoulos C et al. Positive screening for autism in ex-preterm infants: Prevalence and risk factors. Pediatrics 2008 Apr; 121:758.*

*Six percent of infants with confirmed hearing impairment had CMV infections.*

Congenital cytomegalovirus (CMV) infection is associated with sensorineural hearing loss and is the leading nongenetic cause of hearing impairment in infants, but the majority of newborns infected with CMV do not have any clinical signs of CMV disease. To examine the incidence of CMV infection among infants with hearing loss, researchers reviewed the charts of 79,047 infants who were born at one hospital in Texas during a 5-year period in which urine cultures for CMV were performed in all newborns who did not pass hearing screening tests.

Of 572 newborns who did not pass screening tests, 256 infants (0.3% of those screened) had hearing loss that was confirmed by subsequent testing. CMV infection was detected in 16 of these patients (6% of infants with hearing loss). Of the 16 infants with confirmed hearing loss and CMV infection, 4 had clinical signs that suggested congenital infection, but the failed hearing test was the only manifestation of congenital CMV infection among the remaining 12 infants.

**Comment:** This rather simple study might have important implications for clinicians. When newborns fail hearing screening tests, a repeat screen is recommended but sometimes is not completed until the infant is several weeks old.

## Congenital Hearing Loss and CMV Infection

Because the diagnosis of congenital CMV infection can be made with certainty only during the first 2 to 3 weeks of life, clinicians should consider ordering a urine CMV culture before the infant is 3 weeks old. Whether or not to treat infants with congenital CMV infection remains controversial. Therefore, a positive culture would not be an indication for treatment with ganciclovir, but the result would help parents understand the etiology of any hearing loss. The importance of early diagnosis might increase as more data are available about the efficacy of treatment. Of note, nearly half of infants with CMV-related hearing loss pass the newborn hearing screen, but their hearing deteriorates afterward, and hearing loss shows up in later testing.

— Howard Bauchner, MD, and Peggy Sue Weintrub, MD

**CITATION(S):**

Stehel EK et al. Newborn hearing screening and detection of congenital cytomegalovirus infection. *Pediatrics* 2008 May; 121:970.

## Is Infant Formula Too Sweet?

*One organic infant formula has come under scrutiny because it is sweetened with cane sugar.*

According to the New York Times, Similac Organic infant formula represented 36% of all organic formula sales in 2007 — its first full year on the market. Recently, however, the formula has come under scrutiny because it is sweetened with cane sugar (also known as sucrose).

Added sugars in infant formulas help infants digest the protein from cow's milk or soy. Since the 1950s, sucrose has been gradually replaced by lactose in infant formulas, but it still can be found in all major brands of lactose-free and soy formulas. The FDA says that sucrose is safe and that it doesn't regulate which type of sugar is used in formulas. Pediatricians worry that sucrose is more likely than other sugars to erode tooth enamel and that its sweeter taste will lead to overeating during the first year of life and a lifetime preference for sweeter foods, both of which can be predisposing factors to later childhood obesity. Some studies have shown that animals crave sucrose more than fructose and glucose.

So why would Abbott Laboratories choose to use cane sugar in organic formula? Cost is the most likely reason, since lactose derived from organic milk is expensive. Others argue that once infants get used to the sweet taste, they might resist a switch to other brands. When the New York Times commissioned a professional tasting panel to taste eight formulas, Similac Organic was reported to be the sweetest (as sweet as grape juice or Country Time lemonade), whereas the other brands were likened to unsweetened apple juice.

**Comment:** With the increase in childhood obesity, the importance of ingredients in infant food and formula increases. Excessive intake of high-fructose corn syrup has been linked with obesity, cardiovascular disease, and renal disease epidemics. All soy-based and lactose-free formulas are sweetened with both corn syrup solids and sucrose. In the European Union, use of sucrose in infant formula will be banned by the end of 2009. In the U.S., the FDA needs to regulate the amount and type of sweetener in infant formulas. Pediatricians must educate parents about reading food labels and understanding the types of sweeteners,

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## Risk Factors for Starting to Binge or Purge in Adolescents

proteins, and fats that are added to foods. “Cane sugar” sounds much more natural and healthy than it actually is — sucrose, the sweetest of the sugars.

— Robin Drucker, MD

### CITATION(S):

Moskin J. For an all-organic formula, baby, that's sweet. *New York Times*. May 19, 2008. (<http://tinyurl.com/58v7nq>)

*Risk factors for eating disorders differ by age, sex, and type of eating disorder behavior.*

Previous studies have demonstrated that age, sex, teasing about weight, the media, and parental history of an eating disorder are risk factors for eating disorders in children. In a prospective cohort study, researchers examined whether any of these risk factors are independently associated with starting to binge, purge, or both. About 7000 girls and 5500 boys aged 9 to 15 years at baseline received a questionnaire every 12 to 18 months for 7 years as part of the Growing Up Today Study. During the study, 10% of girls and 3% of boys reported either bingeing or purging at least once per week. Bingeing was slightly less prevalent than purging among girls (4.3% vs. 5.3%) and more prevalent than purging in boys (2.1% vs. 0.8%).

Predictors of binge eating in girls were frequent dieting, high level of concern about weight, and trying to look like peers in the media. Age, negative comments about weight from males, and maternal history of an eating disorder were not significant risk factors for binge eating in girls. However, age was a significant independent predictor of purging in girls. Girls who were frequent dieters and younger than 14 years were seven times more likely to purge than girls their age who did not diet, and those aged 14 years and older who dieted were three times more likely to purge than girls their age who did not diet. Similarly, having a mother with an eating disorder was a significant risk factor for purging among girls younger than 14 but not among those aged 14 years and older.

Predictors of binge eating in boys were concern about weight and negative comments about weight from fathers. Predictors of purging in boys were frequent dieting, high level of concern about weight, weight of importance to peers, and negative comments about weight from fathers.

**Comment:** The media's preoccupation with thinness often has been blamed as one cause of eating disorders. This study, however, indicates that a child's peers, parents' behavior, and their own thoughts about their weight might have just as much influence. When counseling families and children about proper nutrition and risk for obesity, we need to be cognizant not to focus on the child's weight but instead on teaching appropriate eating and exercise habits and trying to make parents aware about how their behavior and comments can affect their children's eating behavior, especially during adolescence.

— Robin Drucker, MD

### CITATION(S):

Field AE et al. Family, peer, and media predictors of becoming eating disordered. *Arch Pediatr Adolesc Med* 2008 Jun; 162:574.

## How Young Is Too Young for Intensive Care?

*Outcomes of very premature infants who received intensive care were predicted better by the combination of gestational age, sex, use of antenatal steroids, singleton birth, and birth weight than by gestational age alone.*

One of the most difficult clinical decisions is whether to initiate intensive care for extremely premature infants. Although this decision generally is made by neonatologists, the basis for decisions must be clear. Currently, the most important determinants are gestational age and parental wishes, but ascertainment of gestational age is not an exact science. To examine other factors that predict outcome in extremely premature infants, researchers prospectively studied a large cohort of infants born at 22 to 25 weeks' gestation.

Of 4446 infants born in 19 U.S. centers, 3702 received intensive care (in the form of mechanical ventilation). Infants who received intensive care had a mean gestational age of 24.2 weeks and a mean birth weight of 670 g. At a corrected age of 18 to 22 months, 42% had died, 53% had died or had profound neurodevelopmental impairment, and 67% had died or had any neurodevelopmental impairment. Factors that reduced the risk for death, profound neurodevelopmental impairment, or any neurodevelopmental impairment among infants who received intensive care were use of antenatal corticosteroids, singleton birth, female sex, and increased birth weight (per 100-g increment). Each of these factors was associated with a reduction in risk similar to that associated with a 1-week increase in gestational age. These four factors in addition to gestational age better predicted outcomes of infants who received ventilation than gestational age alone.

**Comment:** This study reminds us that more than gestational age determines the outcome of extremely premature infants. Clinicians who make decisions about initiating intensive care in such infants might find the Web-based tool cited by the authors helpful. However, the authors caution that differences in outcomes at individual centers must be considered when using the tool. The data also reinforce the importance of antenatal steroids. At an estimated cost of US\$3400 per day for neonatal intensive care, finding a way to prevent prematurity would be better.

— William P. Kanto, Jr., MD

### CITATION(S):

Tyson JE et al. Intensive care for extreme prematurity — Moving beyond gestational age. *N Engl J Med* 2008 Apr 17; 358:1672.

## We Worry About Jaundice in Young Infants, but Maltreatment Is a Bigger Problem

*Of 905,000 substantiated maltreatment cases in 2006, 10% were reports of nonfatal maltreatment in infants younger than 1 year.*

Child abuse is a major cause of morbidity and mortality in the pediatric population, and prevention requires an understanding of high-risk ages and circumstances. To examine the risk for nonfatal maltreatment among infants, CDC investigators analyzed cases reported to the National Child Abuse and Neglect Data System.

From October 2005 to September 2006, 905,000 cases of maltreatment were substantiated by child protective services. Of these, 91,278 were infants younger than 1 year who experienced nonfatal maltreatment (annual rate, 23.2/1000

population). Among maltreated infants (52% male), 44% were white, 25% were black, 19% were Latino, 1% were Native American, and 1% were Asian. About 40% of infants were younger than 1 month, and 84% of infants younger than 1 month were younger than 1 week. Neglect was the form of maltreatment in 66% of infants younger than 1 week. Most (60%) cases of maltreatment among infants younger than 1 week and younger than 1 month were reported by medical personnel. Only 32% of reports among infants younger than 1 year were made by medical personnel, indicating that most reports among infants younger than 1 year were made by law enforcement and social service personnel. The CDC editorial note suggests that the high concentration of neglect reports during the first week of life results from maternal and newborn drug testing.

**Comment:** These numbers are chilling. Even if most cases of maltreatment that are identified during the first week of life result from referral for maternal and newborn drug testing, nearly 4000 (13%) maltreated infants younger than 1 week were victims of physical abuse. This form of abuse often results in shaken baby syndrome or head trauma, which can cause death or severe physical injury. Although hospital-based parent education programs have been shown to reduce abuse, I am concerned that we are not focused enough on preventive measures. We place a great deal of emphasis on identifying infants at risk for hyperbilirubinemia during the initial hospitalization and within 48 to 72 hours of discharge. Maybe a similar focus is needed on counseling parents about abuse. The number of physically abused children is far in excess of the reported numbers of infants with kernicterus.

— William P. Kanto, Jr., MD

**CITATION(S):**

*Centers for Disease Control and Prevention (CDC). Nonfatal maltreatment of infants — United States, October 2005–September 2006. MMWR Morb Mortal Wkly Rep 2008 Apr 4; 57:336.*

*A dose–response relation was found between severity of iron deficiency and behavioral outcomes in infants.*

Although the prevalence of iron deficiency anemia in infants and toddlers in the U.S. has decreased during the past 30 years, poor, minority, and immigrant young children continue to be at risk for iron deficiency with and without anemia. More than 25 years ago, researchers reported improved mental development scores in infants with iron deficiency anemia 1 week after they received intramuscular iron. The authors of the current study postulated that only a behavior change in affect or attention could explain such a rapid improvement in cognition. Therefore, they examined the effects of iron status in 77 full-term black infants (age range, 9–10 months) who did not have prenatal or perinatal problems and were recruited during routine visits at an inner-city clinic in Michigan.

Iron deficiency was defined as two or more abnormal iron measurements, in addition to transferrin saturation and ferritin abnormalities, with or without anemia (hemoglobin <11.0 g/dL). Iron sufficiency was defined as hemoglobin ≥11.5 g/dL. The study group included 28 infants with iron deficiency with anemia, 28

## Behavioral Effects of Iron Deficiency With and Without Anemia

with iron deficiency without anemia, and 21 iron-sufficient infants. Neurobehavioral assessment at 9 and 12 months included standardized parent questionnaires and behavior rating scales. Videotaped behavior (free play with toys in the mother's presence) was coded quantitatively at 12 months in 57 infants. All infants received a 3-month supply of an oral iron supplement (2–3 mg/kg/day of elemental iron).

At the initial assessment, poorer iron status was correlated linearly with increasing shyness and decreasing orientation-engagement and soothability. At the 12-month behavioral observation, poorer iron status was associated with less-positive affect and longer time to engage with the examiner. Because only 58% of infants returned for a 12-month blood sample, hematologic response to iron supplementation could not be assessed.

**Comment:** The relation between increasing severity of iron deficiency and behavioral outcomes was characterized by increasing shyness and decreasing orientation-engagement, soothability, positive affect, and engagement in imitative play. Although the authors could not examine the effect of iron supplementation on behavior, prevention trials have reported that infants who did not receive supplemental iron were less likely to show positive affect or to interact socially. These findings support the authors' hypothesis that altered affect and response to novelty are fundamental behavioral deficits in early iron deficiency. These deficits are associated with poor overall developmental outcomes: Iron-deficient infants cannot elicit or benefit from nurturing interactions that foster optimal early development. Unfortunately, none of the multiple hematology tests (including ferritin) differentiated iron deficiency with and without anemia. Nevertheless, screening for anemia and providing an iron supplement to infants with even borderline hemoglobin levels seem prudent.

— *Martin T. Stein, MD*

**CITATION(S):**

*Lozoff B et al. Dose-response relationships between iron deficiency with or without anemia and infant social-emotional behavior. J Pediatr 2008 May; 152:696.*

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1. Alves-Rodrigues A, Shao A. The science behind lutein. *Toxicol Lett.* 2004;150:57-83. 2. Rapp LM, Maple SS, Choi JH. Lutein and zeaxanthin concentrations in rod outer segment membranes from perifoveal and peripheral human retina. *Invest Ophthalmol Vis Sci.* 2000;41:1200-1209. 3. Khachik F, Bernstein PS, Garland DL. Identification of lutein and zeaxanthin oxidation products in human and monkey retinas. *Invest Ophthalmol Vis Sci.* 1997;38:1802-1811. 4. Birch EE, Castañeda YS, Wheaton DH, Birch DG, Uauy RD, Hoffman DR. Visual maturation of term infants fed long-chain polyunsaturated fatty acid-supplemented or control formula for 12 mo. *Am J Clin Nutr.* 2005;81:871-879. 5. Birch EE, Hoffman DR, Castañeda YS, Fawcett SL, Birch DG, Uauy RD. A randomized controlled trial of longchain polyunsaturated fatty acid supplementation of formula in term infants after weaning at 6 wk of age. *Am J Clin Nutr.* 2002;75:570-580. 6. Food and Nutrition Board, Institute of Medicine, National Academy of Sciences. Dietary Reference Intakes for Vitamin A, Vitamin K, Arsenic, Boron, Chromium, Copper, Iodine, Iron, Manganese, Molybdenum, Nickel, Silicon, Vanadium, and Zinc. Washington, DC: National Academy Press; 2001:82-85.

**Wyeth**



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