This chapter in the *Yearbook on Nutrition and Growth* summarizes the articles that have been published in the area of cognition and nutrition. Articles were included if published (including E-pub ahead of press) between the dates July 1, 2012 and June 30, 2013. All studies were human observational or clinical trials. The topics or nutrients explored in the articles naturally fell into one of three categories: feeding studies (breastfeeding and school feeding), long-chain polyunsaturated fatty acids supplementation (LCPUFA) and micronutrients (methyl donors and iodine, iron and vitamin A). Comments are included following the summaries of papers within each category.

### Feeding Studies: Infant Feeding

**Role of breastfeeding in childhood cognitive development: a propensity score matching analysis**

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**Background:** Children that have been breastfed score higher on IQ tests when compared to children who were formula-fed. Some suggest the beneficial effect from breastfeeding is an artifact of...
the situation. Women who decide to breastfeed differ from women who decide to use formula. The purpose was to explore the association between breastfeeding and offspring cognitive scores to determine if the relationship is direct or due to confounding variables.

**Methods:** A novel statistical analysis, propensity score matching (PSM), was used to analyze data from the Early Childhood Longitudinal Study, Birth Cohort. PSM approximates a randomized research design using observational data by matching data from two groups. Children who were breastfed were matched on several different potentially confounding variables to children who were fed commercial infant formula. A total of 10,700 mother-child pairs were used in this analysis. The Bayley Short Form-Research Edition (BSF-R) was used to assess cognitive function when the offspring were 2 years old.

**Results:** Initially, nine of the twelve potential confounding variables differed between groups. After matching, group differences remained for only one variable (a small difference in birth weight). After reducing differences between groups for confounding variables, the effect of breastfeeding on cognitive scores was calculated. Prior to matching, the association between breastfeeding and cognition was significant (mean difference 3.20; \( p \leq 0.05 \)). After matching, the significance remained but was attenuated by 40% (mean difference 1.92; \( p \leq 0.05 \)).

**Conclusion:** Using PSM, the beneficial effect of breastfeeding on offspring cognition is supported. Further research is needed to understand the pathways for this effect.

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**Infant feeding: the effects of scheduling vs. on-demand feeding on mothers’ wellbeing and children’s cognitive development**

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_Eur J Public Health_ 2012; 23: 13–19

**Background:** Two predominate infant feeding styles are feeding on demand or feeding to a schedule. Proponents of feeding to a schedule suggest this feeding style leads to a happier baby that sleeps through the night earlier, lowers the level of parental stress and provides neurocognitive developmental advantages. The purpose was to compare children’s long-term cognitive development and academic performance based on maternal self-identified infant feeding style.

**Methods:** Participants were part of the Avon Longitudinal Study of Parents and Children. A total of 10,419 mother-child pairs were grouped as ‘on demand’ or ‘scheduled’ feeders for this analysis based on mothers’ answers at 4 weeks post-partum to the questions: *‘Is your baby fed on a regular schedule?’* At 8 years of age, cognitive development was assessed by IQ tests and academic performance scores were determined with the Standard Attainment Test (SAT). The SAT is standardized for use in children from the age of 5 to 14 years.

**Results:** After controlling for multiple confounding variables, infants fed to a schedule had lower SAT scores at all ages and lower IQ scores (~4 points) at 8 years of age compared to those fed on demand.

**Conclusion:** Differences were found between groups based on maternal identified feeding style. Children fed on demand during infancy had higher cognitive and academic performance scores when compared to children fed to a schedule during infancy. Further testing controlling infant feeding style is needed to explore these results.
The study of Boutwell et al. asks an old question: Is higher IQ consistently observed in breastfed compared to formula-fed infants due to the composition of human milk or some other environmental benefit associated with feeding choice. Unlike past studies, they used a novel statistical approach (propensity score matching) to examine a very large US birth cohort of 10,700 mother-child pairs. They observed an effect on the Bayley Short Form that was 3.2 points higher in breastfed infants before matching the groups for differences in potentially confounding variables. This is similar to a 4-point advantage that has been found quite consistently with the Bayley Scales of Infant Development Mental Developmental Index (BSID MDI). After matching for all but one potentially confounding variable, the difference between the groups became quite small (1.92 points) but was still statistically significant. All studies that attempt to control for potentially influential variables have the limitation that they may have failed to control for an important unknown variable that could account for this small difference. Moreover, commercial infant formulas continue to be modified to be more similar to human milk in composition and functionality. For example, changes in formula after this cohort completed the first year of life include the addition of DHA and ARA to US formulas (2002) and the inclusion of pre- and probiotics in some formulas (also see the section on LCPUFA for evidence of cognitive benefit of formula LCPUFA supplementation). As a result, it is unlikely that this question will have a definitive answer anytime soon.

Iacovou and Sevilla looked at the relationship between on-demand vs. scheduled feeding in infancy on childhood IQ and academic performance. They found both were higher in 8-year-old children who were fed on demand. We are inclined to read this as evidence that encouraging infant self-regulation can produce important benefits for subsequent child development. As far as we know, this is the first study to evaluate self-regulation in relation to cognitive function or academic performance. We expect it will lead to many more studies on this subject.

**Refined carbohydrate intake in relation to non-verbal intelligence among Tehrani schoolchildren**

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**Background:** Adequate micronutrient consumption is known to be essential for cognitive development. Carbohydrate and in particular glucose and the glycemic index are thought to also in-
fluence cognitive function but few studies exist. The purpose of the study was to examine the relationship between refined carbohydrate intake and intelligence quotient (IQ) in schoolchildren.

**Methods:** 245 children aged 6–7 years from 129 elementary schools in Tehran, Iran, participated. Intelligence was measured by Raven’s Colorful Progressive Matrices and a food frequency questionnaire assessed dietary intake of refined carbohydrates in the last year.

**Results:** Children were divided into tertiles based on the amount of refined carbohydrate consumed. After controlling for potential confounding variables, difference in IQ scores among the tertiles of refined carbohydrate intake were not found, however non-verbal IQ scores and refined carbohydrate intake were inversely related. After adjusting for all potential confounding variables, the negative relationship remained ($\beta = -8.495; p = 0.038$).

**Conclusion:** These data suggest a negative relationship between refined carbohydrate intake and non-verbal intelligence scores in young schoolchildren from Tehran, Iran. Further studies controlling refined carbohydrate intake and assessing intelligence are needed to confirm these findings.

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**The effect of beverages varying in glycemic load on postprandial glucose responses, appetite and cognition in 10- to 12-year-old schoolchildren**

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**Background:** Consumption of breakfast in children is related to higher cognitive performance. A proposed underlying mechanism conferring the beneficial effect is postconsumption stabilized glucose levels. The impact of breakfast varying in glycemic load (GL) on cognition is unknown. The purpose was to assess the effect of a breakfast drink with varying levels of carbohydrate relative to fat and protein on cognitive function.

**Methods:** 40 children aged 10–12 years participated in this double-blind, randomized, three-way repeated measures crossover design study. Three isoenergetic drinks were given: a glucose beverage (glycemic index (GI) 100, GL 65), a full milk beverage (GI 27, GL 5) and a half milk/glucose beverage (GI 84, GL 35). For the next 3 h, cognition was tested hourly. Six cognitive constructs were assessed: speed of processing, attention switching, perceptual speed, short-term and working memory, and inspection time. Blood glucose levels were monitored throughout with a Continuous Glucose Monitoring System (CGMS).

**Results:** Blood glucose AUC differed between conditions as expected ($p < 0.001$). No main effects were found for test drink on any of the cognitive assessments. A significant interaction was detected between gender and drink GL for short-term memory. A greater number of words were recalled by girls when they consumed either milk containing beverage (0.7–0.8 words) compared to the glucose beverage (0.5 words; $p \leq 0.014$).

**Conclusion:** No effect on cognitive performance was found when GL was varied in a breakfast drink for the group as a whole, however girls had higher short-term memory scores after consuming the two protein-containing beverages compared to glucose alone.
Effects of lunch on children’s short-term cognitive functioning: a randomized crossover study

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Background: Skipping breakfast is related to poorer cognitive performance in schoolchildren though the impact of skipping lunch on cognitive performance has only been investigated in adults. European schools commonly last for a full day, however students do not consistently consume lunch. The purpose of this study was to investigate the effect of consuming lunch on cognitive performance.

Methods: 105 sixth grade children participated in this randomized, crossover controlled trial. The study took place at an all-day school in Germany that served warm lunches. There were 2 test days separated by 1 week. On 1e day, children were tested after skipping lunch and another after having lunch. Classes were randomized to test order. Cognitive assessment occurred immediately following the lunch break. The computerized test battery of the Vienna Test System and its subtests assessed alertness, immediate block span (visuospatial performance) and selective attention.

Results: After adjustment for multiple testing, no differences between groups were found for any of the cognitive tests.

Conclusion: Skipping lunch had no adverse effect on a short-term measure of cognitive performance in sixth grade children. Further research is needed to verify these results and explore the underlying mechanisms.

Early-stage primary schoolchildren attending school in the Malawian school feeding program (SFP) have better reversal learning and lean muscle mass growth than those attending a non-SFP school

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Background: School feeding programs (SFP) have been adopted in developing countries as a way to improve children’s nutrition, cognitive development and academic performance. Conflicting evidence exists regarding the effectiveness of SFP. The purpose was to assess cognition in children attending a school that was receiving additional nutrition through the SFP in Malawi, Southern Africa.

Methods: Children aged 6–8 years in two rural public primary schools (one SFP school and one non-SFP school) were followed for 1 year. A total of 226 children completed baseline and follow-up testing. Children in the SFP received a daily ration of corn-soy porridge while children in the non-SFP did not. The Cambridge Neurological Test Automated Battery (CAN-TAB) was used to assess the following domains of cognition related to behavior: learning, set-shifting, memory and attention and 3 subtests to assess brain cognitive domains including memory, reversal learning and attention.
Results: A significant improvement in reversal learning was observed in the SFP children between baseline and follow-up testing. The group had a greater reduction in the number of intra-extra pre-dimensional shift errors compared to the non-SFP group (p = 0.02).

Conclusion: Results suggest the additional nutrition provided by SFP is beneficial for short-term cognitive development in children from underdeveloped countries who have poor access to food.

Comments
Two studies published this year looked at carbohydrate quality and cognition in school-children. Abargouei et al. measured intelligence in 6- to 7-year-old Iranian children who were divided into tertiles based on their refined carbohydrate intake. While they did not find any relationship between refined carbohydrate intake and overall IQ, intake was inversely related to non-verbal intelligence scores even after adjusting for potentially confounding variables. More targeted tests of cognitive function might have been a better choice for outcome than IQ, which should be quite stable at this age. Brindal et al. provided 10- to 12-year-old Australian children isocaloric breakfasts that varied in glucose and milk content. While they found no main effects on any of the cognitive assessments, girls performed better on a test for short-term memory (word recall) if they consumed either a milk-containing beverage compared to a beverage that contained only glucose. German sixth grade children participated in a randomized, crossover controlled study of the relationship between lunch consumption and tests to assess alertness, visuospatial performance and selective attention. After adjusting for multiple testing, no differences were found between children’s performance when they ate lunch compared to when they did not. In contrast, Malawian children (6–8 years of age) performed better on the CAN-TAB (which assesses learning, memory and attention, and reversal learning and attention) when given a daily ration of a corn-soy porridge. Both of these studies provided a meal to children who otherwise would likely have been hungry. Both measured a similar cognitive behavior. The difference in results could be due to differences in energy reserves between the two populations or to differences in age, with younger children being more susceptible to hunger.

Long-Chain Polyunsaturated Fatty Acid Studies

Long-term effects of LCPUFA supplementation on childhood cognitive outcomes
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Background: Long-chain polyunsaturated fatty acids (LCPUFA) are thought to play a role in neurocognitive development during infancy. Data vary regarding whether LCPUFA supplementation during infancy results in a positive neurocognitive effect during early childhood. This study reported results for age-appropriate neurocognitive assessment at 6-month intervals between 18 months and 6 years of age in children supplemented with infant formula for 12 months with varying doses of DHA.
**Methods:** 81 children participated in the randomized, double-blind, DHA dose-response controlled trial. Newborn term infants were randomized to one of four groups varying in DHA (0.32, 0.64 and 0.96% of total fatty acids) with 0.64% arachidonic acid (ARA) or control (0% DHA and ARA). Cognitive testing occurred at 18 months of age and every 6 months thereafter until 6 years of age. The cognitive assessments performed at each time point varied and were age-appropriate.

**Results:** No differences between groups were found at 18 months for infant development or early communication skills (MCDI) or BSID MDI or at any time point for tasks of spatial memory, simple inhibition or advanced problem-solving. The middle dose groups (0.32 and 0.64%) had significantly increased rule-learning and inhibition task scores at 4 and 5 years on the Dimensional Change Card Sort (DCCS) task and had greater vocabulary scores at age 5 years (PPVT) compared to the control group. The highest 2 doses (0.64 and 0.96%) had higher scores than the control group on the Stroop test across the ages of 3–5 years. The Stroop tested ability to follow a rule that ran counter to an automatic response. All of these findings were significant when supplemented groups were combined and compared to control. Advantages were found for the combined DHA-supplemented groups compared to control infants on several cognitive tests to 5 years of age as well as on full-scale and verbal IQ at 6 years of age.

**Conclusion:** DHA and AA supplementation in infancy increased cognitive scores to age 6. These results suggest that increasing DHA status early in development benefits cognitive development at school age.

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**Effects of long-chain polyunsaturated fatty acid supplementation of infant formula on cognition and behavior at 9 years of age**

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*Dev Med Child Neurol* 2012; 54: 1102–1108

**Background:** Long-chain polyunsaturated fatty acids (LCPUFA) are thought to be important for early cognitive development, but few studies have assessed neurocognitive development at any time in childhood. This study reported cognitive and behavioral findings in 9-year-olds that received formula supplemented with LCPUFA in infancy and examined the potential confounding effect of perinatal maternal smoking.

**Methods:** The design was a double-blind, randomized control trial. 474 healthy term infants were recruited at birth. Three groups were followed for 9 years: the control group (n = 169) received standard formula (SF), the intervention group (EF; n = 145) received DHA- and AA-enriched formula, and the third group was fed human milk (BF; n = 160). Supplementation duration was birth to 2 months. Mothers reported smoking habits during pregnancy. The Wechsler Abbreviated Scale of Intelligence was administered at 9 years of age. Scores were reported as full IQ (FIQ) and those scores that comprised FIQ: verbal IQ (VIQ) and performance IQ (PIQ). A Developmental Neuropsychological Assessment (NEPSY) was used to assess executive function and memory and learning.

**Results:** Breastfeeding provided benefits regardless of maternal smoking: children exposed in utero to smoking who were BF had greater FIQ and learning and memory scores (p < 0.05) when compared to SF. Offspring exposed to smoking and given EF or BF also had higher VIQ scores when compared to the SF group (p < 0.05). Among non-smoking pregnancies, children who were BF had greater FIQ (p = 0.026) and learning and memory scores (p = 0.012) compared to EF. Subset IQ scores varied by infant nutrition and smoking exposure.
Conclusion: Breastfeeding continues to provide benefits for neurocognitive and behavioral development at 9 years of age. The beneficial effect of LCPUFA enrichment was inconsistent and influenced by maternal smoking.

Effects of high-dose fish oil supplementation during early infancy on neurodevelopment and language: a randomized controlled trial

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Background: Supplementation of long-chain polyunsaturated fatty acids (LCPUFA) during pregnancy and infancy is proposed to have beneficial effects on offspring neurocognitive development. Supplementation studies have found mixed results regarding benefits of LCPUFA supplementation on infant neurocognitive function. This study directly supplemented infants for the first 6 months of life to determine if supplementation improved global infant neurodevelopment and early communication.

Methods: A randomized, double-blind, placebo-controlled trial recruited 420 healthy term infants. The intervention group (n = 218) received DHA-enriched fish oil (250 mg DHA/day and 60 mg EPA/day) and the placebo group (n = 202) received olive oil. At 12 and 18 months, language was assessed by the MacArthur-Bates Communicative Development Inventory (MCDI) and at 18 months the Bayley Scales of Infant and Toddler Development (BSID-III) and the Achenbach Child Behavior Checklist (CBCL) were assessed. The MCDI was repeated at 18 months.

Results: Cord blood fatty acids were analyzed and the results confirmed that both groups had a similar DHA status at birth. At the end of the intervention, the intervention group had greater erythrocyte fatty acid (FA) measured DHA and EPA and lower AA levels (p < 0.05) when compared to the placebo group. No group differences were found for the BSID-III though in a subset analysis of the MCDI, differences were found at 12 and 18 months for language assessments as reflected by higher gesture scores (p < 0.05) in the intervention group.

Conclusion: Global infant neurodevelopment was not improved by early postnatal supplementation of a high dose of LCPUFA. Subset analysis did find greater language skill development in the supplemented group.

Long-chain PUFA supplementation in rural African infants: a randomized controlled trial of effects on gut integrity, growth and cognitive development

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Background: Harsh environmental conditions experienced in third world countries can influence gut integrity causing malabsorption leading to poor growth and development in newborns. Long-
chain polyunsaturated fatty acid (LCPUFA) supplements are associated with a reduction in inflammation and higher neurocognitive development. No study has investigated if LCPUFA can reduce gastrointestinal inflammation and improve neurocognitive development in rural Gambian infants. 

**Methods:** 183 breastfed infants participated in the randomized, double-blind controlled trial. An LCPUFA (DHA and EPA) supplement was given as a capsule of fish oil (2 ml) (200 mg DHA/day and 300 mg EPA/day; n = 92) to infants daily from 3 to 9 months. The control group (CON; n = 91) received olive oil (2 ml). Anthropometrics were used to assess growth and the lactulose:mannitol ratio was used as a marker of gut integrity. Cognitive development was assessed at 12 months using the Willatts’ Infant Planning Test and a single object task attention assessment.

**Results:** Supplementation increased the percentage of DHA and EPA in plasma total lipids (p < 0.001). At 9 and 12 months, mid upper arm circumference and triceps skinfold was greater in the FO group compared to the CON though no differences in weight-for-age or weight-for-length were detected. No differences between groups were found for markers of inflammation, gut integrity or neurocognitive development.

**Conclusion:** Supplementation increased infant n-3 LCPUFA status in Gambian infants. Anthropometric differences were found for markers of adiposity, however no differences were found for markers of inflammation, gut integrity or neurocognitive development.

**Comments**

Four papers published this year evaluated the effects of supplementing infants with long-chain polyunsaturated omega-3 fatty acids. Three of these involved cognitive tests done after supplementation was discontinued for at least 6 months and as long as 9 years. All three were conducted in developed countries. De Jong et al. studied 9-year-old children who had been fed either standard formula or DHA- and ARA-enriched formula for the first 2 months of life. A third group received human milk. Meldrum et al. studied 12- and 18-month-old children who took a DHA-enriched fish oil capsule or a placebo group that took an olive oil capsule for the first 6 months of life. Colombo et al. studied cognitive outcomes in children from 18 months to 6 years of life at 6-month intervals who had received formulas with one of four concentrations of DHA during the first 12 months of life – 0, 0.32, 0.64 and 0.96% DHA of total dietary fatty acid (the DHA-containing formulas also provided 0.64% ARA).

Full-scale (FIQ) and verbal IQ (VIQ) were measured at school age by both de Jong et al. and Colombo et al. Children supplemented with DHA and ARA had higher FIQ and VIQ at 6 years in the latter study. VIQ was significantly higher in the de Jong et al. study with formula containing DHA and ARA compared to standard formula only among offspring of women who smoked. A major difference between these studies was the duration of feeding of supplemented formula in infancy. Both suggest benefits to verbal IQ at school age. Other targeted cognitive outcomes found to be higher in DHA- and ARA-supplemented children by Colombo et al. included higher scores on the PPVT at 5 years and on tests that required the child to follow a rule counter to an automatic response (Stroop) or inhibit a learned rule (DCCS). An earlier report from this cohort of children found higher sustained attention at 9 months of age in the combined supplemented groups compared to the control group.

In agreement with Meldrum et al., Colombo et al. found no effect of DHA and ARA in infant formula on the MCDI and the BSID-III at 18 months of age. Both studies concluded that global toddler neurodevelopment was not improved by early postnatal supplementation. Meldrum et al. did find a suggestion that early communication (based on gestures) was enhanced by fish oil supplementation. It would be interesting to see more targeted tests of cognition and standardized IQ tests in Meldrum’s cohort as these children reach school age. The results could offer some insight into the role of intrauterine exposure; the cord blood DHA level in these children indicated
exposure was much higher than in the USA and duration of DHA and ARA supplementation in infancy.

Van der Merwe et al. studied breastfed infants supplemented with either fish oil capsules or olive oil from 3 to 9 months of age. Cognitive development was assessed at 12 months of age using two tests. No differences were observed between the two groups, however an effect cannot be ruled out because the Willatt’s test was given when children were quite old and the duration of supplementation was relatively short.

In summary, the study of Colombo et al. suggested that global tests of language and other aspects of development at 18 months do not capture positive effects of DHA and ARA supplementation even though higher performance on more targeted tests was found in infancy and later in childhood. The two studies that provided fish oil as capsules to infants found more DHA in circulating lipids (plasma or erythrocyte), but the large dose of fish oil provided did not prevent a decline in DHA from that found in cord erythrocytes in one study. Not only was the duration of supplementation shorter, but the amount of DHA absorbed may have been much less than from infant formula in the study by Colombo et al.

Micronutrient Studies: Methyl Donors

Choline intake during pregnancy and child cognition at age 7 years

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Am J Epidemiol 2013; 177: 1338–1347

Background: Choline, B12, folate and betaine are methyl donors that are proposed to be important for early development and function of the central nervous system. For example, animal models have shown that choline is important for cholinergic transmission and that choline improves offspring memory. The purpose of this study was to assess the relationship between methyl donors in maternal diet during the second trimester and cognition in the offspring at 7 years of age.

Methods: The sample was drawn from participants in the prospective observational longitudinal Project Viva cohort designed to examine the impact of prenatal exposures on offspring growth and development. Enrollment occurred at the first obstetric office visit. At the first- and second-trimester study visits, a food frequency questionnaire was used to collect maternal dietary data. At age 7 years, offspring completed the Wide Range Assessment of Memory and Learning Second Edition (WRAML2), the Design and Picture Memory subtests (assesses visuospatial memory) and the Kaufman Brief Intelligence Test, Second Edition (KBIT-2) to assess verbal and non-verbal IQ. Mothers completed the KBIT-2 as well, and the maternal KBIT-2 score was used as a covariate in the analyses.
**Results:** A total of 895 mother-child pairs completed this study. After controlling for confounding variables, maternal choline intake during the second trimester was related to offspring WRAML2 scores. Children exposed in utero to the highest quartile of choline intake when compared to the lowest quartile of intake, had scores that were 1.4 points greater. Associations with cognitive test scores were found in separate bivariate models for B12, betaine and folate, however, the effect disappeared when all were included in one model. Other associations approached significance including a positive relationship between first-trimester maternal choline intake and WRAML2 (£ = 0.08) and second-trimester maternal choline intake and the child’s non-verbal KBIT-2 score (£ = 0.06).

**Conclusion:** Second-trimester maternal choline intake was related to improved offspring memory score at age 7 years. No other nutrients were related to offspring cognition. Measurement of these methyl donors in maternal serum would be of interest to determine if these can be used as biomarkers for intake.

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**Phosphatidylcholine supplementation in pregnant women consuming moderate choline diets does not enhance infant cognitive function: a randomized, double-blind, placebo-controlled trial**

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**Background:** Choline is an essential nutrient important for fetal neurocognitive development. Safety of choline supplementation and optimal levels needed to ensure appropriate fetal neurocognitive development is unknown. The purpose was to assess the safety and efficacy of choline supplementation during pregnancy and breastfeeding and determine the relationship between choline supplementation and early infant cognitive development.

**Methods:** 140 pregnant women participated in this randomized, double-blind controlled trial. Participants were randomized to the intervention (CHL; 750 mg choline/day) or to the control group (CON; consumed equivalent amounts of corn oil). Women who consented for the study were asked to consume the gel caps from 18 weeks of gestation to 90 days postpartum and planned to breastfeed for £90 days. Maternal choline intake was estimated from 3-day food records obtained at 30 weeks of gestation and 45 days postpartum. Infant cognitive testing occurred at 10 and 12 months. Short-term visuospatial memory, long-term episodic memory using an imitation paradigm, language development (MacArthur-Bates Short Form Vocabulary Checklist Level I) and global development (The Mullen Scales of Early Learning) were assessed.

**Results:** No differences between groups were found for cognitive tests. All infants were breastfed for a minimum of 45 days. No differences between groups were found for adverse events related to choline supplementation. Maternal dietary intake of choline at 30 weeks of gestation and 45 days postpartum did not differ between groups and represented ~80% of recommended intake during pregnancy and 65% of recommended intake during breastfeeding.

**Conclusion:** Supplementation above and beyond recommendation did not provide offspring neurocognitive developmental advantages at 10 and 12 months. There were no adverse events
related to choline supplementation in this population. Future studies should assess maternal serum values for nutrients and have a longer follow-up period for offspring cognitive assessment.

**Serum folate but not vitamin B_{12} concentrations are positively associated with cognitive test scores in children aged 6–16 years**

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*J Nutr 2013; 143: 500–504*

**Background:** There is limited evidence suggesting that folate and B_{12} are important for infant cognitive development. Few studies have explored if micronutrient status is related to cognitive performance in childhood. The purpose was to examine the relationship between folate and B_{12} status and cognitive function in 6- to 16-year-olds.

**Methods:** These data were part of the NHANES III (1988–1994) cohort studied prior to widespread fortification of folate in food. This survey is a representative cross-sectional randomly sampled population from the United States. A total of 5,365 children had blood folate and B_{12} analysis. The Wechsler Intelligence Scale for Children-Revised (WISC-R) and the Wide Range Achievement Test-Revised (WRAT-R) were administered by trained personnel to test cognitive function.

**Results:** A positive association was found between folate status and reading and block design scores after adjusting for potential confounders. When compared to the reference population, those with folate levels in the fourth quartile had reading scores that were 3.28 points higher and block design scores that were 0.64 points higher. No association was found between B_{12} and any of the cognitive tests.

**Conclusion:** This was the first study to assess serum micronutrient levels in relation to cognition in children. Higher folate but not vitamin B_{12} status related to higher cognitive performance.

**Cobalamin and folate status predicts mental development scores in North Indian children 12–18 months of age**

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**Background:** Micronutrient deficiencies can impair infant neurocognitive development. This is more common in poor countries with limited access to proper infant nutrition or where maternal
vegan diets are common. The purpose was to examine the relationship between infant serum status for folate, B\textsubscript{12}, total homocysteine and methylmalonic acid and cognitive scores in North Indian infants.

**Methods:** These outcomes were secondary aims of a parent trial to assess the effectiveness of zinc supplementation on illness rate. 571 children were assessed between 12 and 18 months of age and again 4 months later. Blood was collected at the first visit and subsets of the Bayley developmental index (Mental Development Index (MDI) and Psychomotor Development Index (PDI)) were administered at both visits to assess cognitive development.

**Results:** Zinc supplementation had no effect on cognition in the primary study. Higher serum homocysteine and methylmalonic acid concentrations predicted lower MDI at follow-up: For every twofold increase in the concentrations of homocysteine and methylmalonic acid, the MDI scored decreased by 2.0 (95% CI 0.5–3.4; p = 0.007) and 1.1 (95% CI 0.3–1.8; p = 0.004), respectively. Folate predicted MDI at baseline and follow-up (β = 1.3, p = 0.02 and β = 1.6, p = 0.003, respectively) only in those infants with a serum B\textsubscript{12} status >25th percentile.

**Conclusion:** Higher levels of homocysteine and methylmalonic acid are related to poorer infant neurocognitive development. Folate was related to better cognitive scores only in those infants with a higher B\textsubscript{12} status. Trials are needed to test the effectiveness of B\textsubscript{12} and folate supplementation on cognitive development in children at risk for deficiency. A risk factor for B\textsubscript{12} deficiency may have been continued breastfeeding. 74% were still breastfed at a mean of 14.9 months.

**Maternal intake of methyl-donor nutrient and child cognition at 3 years of age**

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**Background:** Methylation reactions are important for development and function of the nervous system. Nutrients that act as methyl donors (B\textsubscript{12}, folate, choline and betaine) have been suggested to be important for neurocognitive development. The purpose of this study was to assess the maternal dietary intake of methyl-donor nutrients during pregnancy and compare them to values to offspring cognitive development at age 3 years.

**Methods:** Women were participants in the prospective observational longitudinal Project Viva cohort designed to examine the impact of prenatal exposures on offspring growth and development. Women were enrolled early in pregnancy and food frequency questionnaires were used to collect maternal dietary data throughout pregnancy. At 3 years of age, offspring completed the Peabody Picture Vocabulary Test III (PPVT-III) and the Wide Range Assessment of Visual Motor abilities (WRAVMA).

**Results:** A total of 1,210 participants were included in this analysis. When controlling for confounding variables, maternal folate intake from food and supplements during the first trimester was related to offspring PPVT-III scores. A 600 μg/day increase in maternal folate intake was associated with an increase of 1.6 points on the PPVT-III. A small negative association was observed between maternal second-trimester vitamin B\textsubscript{12} intake and the PPVT-III. For every increase of maternal B\textsubscript{12} intake by 2.6 μg/day, a 0.4-point score decrease was predicted for the PPVT-III. No relationship was found between any methyl-donor nutrient and the score on the WRAVMA.
Conclusion: Maternal dietary folate intake was related to improved neurocognitive scores in offspring in early childhood. Future studies assessing serum levels of maternal methyl-donor nutrients are needed to confirm these findings.

Comments Five papers published this past year studied status of methyl donors (choline, betaine, folate and vitamin B₁₂) and cognition. A cohort of 6- to 16-year-old children from NHANES III (before widespread fortification of food with folate) was evaluated for a relationship between serum folate or vitamin B₁₂ and cognition. Serum folate but not vitamin B₁₂ concentration was related to higher cognitive performance. Similarly, higher serum folate was related to higher BSID MDI scores in a study of North Indian infants and toddlers in those with a vitamin B₁₂ concentration above the 25th percentile. However, higher homocysteine and methylmalonic acid (both associated with low methyl donor status) were associated with lower BSID MDI scores. Villamor et al. estimated methyl donor intake in pregnant Bostonian women from food and supplements in the Project VIVA cohort (1,210 participants) and child cognitive performance at 3 years of age. Scores on the PPVT-III were higher with higher maternal folate intake in the first trimester of pregnancy, however maternal vitamin B₁₂ intake was associated with a small decrease in the PPVT-III. Boeke et al. estimated maternal intake of methyl donors in the second trimester and compared this to offspring cognition at 7 years measured by the WRAML2 and other cognitive tests. Choline intake, but not intake of other methyl donors, correlated with higher memory at 7 years. Cheatham et al. supplemented pregnant women with choline (750 mg/day) during the last half of pregnancy and the first 3 months of lactation but did not find any neurocognitive development advantage at 10 and 12 months although women in the study consumed good amounts of dietary choline.

Several of these studies support the idea that low maternal methyl donor intake, particularly folate and choline, during intrauterine development result in lower developmental scores, however future studies should control for socioeconomic status as intake of folate and vitamin B₁₂ and possibly other methyl donors is linked to income and education.

Micronutrient Studies: Iron, Vitamin A and Iodine

Iron-deficiency anemia in infancy and poorer cognitive inhibitory control at age 10 years

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Background: Iron is an important micronutrient for brain development, specifically the regions of the brain related to inhibitory control and response inhibition. It is unknown if exposure to iron-
deficiency anemia (IDA) during infancy impairs these functions long term. The purpose of the study was to compare cognitive performance of 10-year-olds diagnosed with compared to without IDA during infancy on tasks that assess executive function.

Methods: This was a follow-up to a study assessing the behavioral, developmental and neurofunctional effects of IDA during infancy in a Chilean population. Anemia was defined as hemoglobin <100 g/l at 6 months or <110 g/l at 12 or 18 months of age. IDA was treated with 15 or 30 mg/day of iron depending on age. Children with IDA at age 10 were excluded from the study. A go/no-go task assessed inhibition and event-related potentials (ERPs), electro-oculography and electroencephalography were recorded.

Results: When compared to children without IDA during infancy, children diagnosed with IDA during infancy had slower reaction times, decreased accuracy, longer latency to the N2 peak and a smaller P300 amplitude.

Conclusion: Children exposed to IDA during infancy showed poorer scores on neurocognitive tests. These findings suggest that even when anemia is corrected early, IDA leads to cognitive deficits in childhood.

Cognitive and motor skills in school-aged children following maternal vitamin A supplementation during pregnancy in rural Nepal: a follow-up of a placebo-controlled, randomized cohort

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Background: Retinoic acid is vital for fetal neural development, in particular for neural tube formation, neuron development and synaptic signaling. Vitamin A deficiency is common in poor pregnant women from underdeveloped countries. The purpose is to examine the long-term impact of perinatal vitamin A supplementation on offspring cognitive and motor development at 10–13 years of age.

Methods: The original study was a cluster randomized, placebo-controlled trial. Married women of reproductive age were randomized by village to treatment (TRT) or control (CON). The TRT group received weekly oral doses of vitamin A (7,000 μg retinol equivalents) during a continuous period of 3.5 years. Cognition was assessed using the Universal Nonverbal Intelligence Test (UNIT) and Movement Assessment Battery for Children (MABC) assessed motor ability.

Results: 390 children completed follow-up. No group differences were found for UNIT (mean difference –1.07; p = 0.78) or MABC scores (mean difference 0.18; p = 0.15), however a greater proportion of children in the CON had repeated a grade when compared to the TRT group (28 vs. 16.7%; p = 0.01), suggesting some functional impairment.

Conclusion: At 10 to 13 years of age, no effect of vitamin A supplementation during pregnancy on cognitive or motor development was found. Periconceptual vitamin A supplementation was not effective at improving neurocognitive or motor skills in offspring in childhood.
Effect of inadequate iodine status in UK pregnant women on cognitive outcomes in their children: results from the Avon Longitudinal Study of Parents and Children (ALSPAC)

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Background: Iodine is crucial for fetal neurocognitive development. Iodine deficiency may be present in otherwise well-nourished populations. The purpose was to examine the relationship between maternal iodine status during early pregnancy and offspring neurocognitive development in the UK.

Method: Data were drawn from the Avon Longitudinal Study of Parents and Children. A total of 1,040 mother–child pairs were used for this analysis. Urinary iodine concentration was measured late in the first trimester (median 10 weeks) and creatinine was used to correct for urine volume (iodine:creatinine ratio). The maternal iodine:creatinine ratio was dichotomized to values <150 μg/g (deficient) or ≥150 μg/g (sufficient). The Wechsler Intelligence Scale for Children was used to assess offspring IQ at 8 years of age. One year later, the Neale Analysis of Reading Ability was administered to test reading speed, accuracy and comprehension.

Results: A greater proportion of children born to mothers with iodine deficiency in the first trimester of pregnancy had suboptimal cognitive performance compared to children born to mothers who were iodine-sufficient. After adjusting for all known confounding variables, offspring exposed to iodine deficiency were 1.4–1.69 times more likely to have scores in the lowest quartile for verbal IQ, reading accuracy and reading comprehension (p < 0.03). When the deficient iodine category was subdivided further (<50 or 50–150 μg/g), cognitive scores were worse with decreasing maternal iodine status.

Conclusion: Poor maternal iodine status early in pregnancy is associated with impaired cognitive development in offspring during childhood. Further studies controlling maternal intake of iodine during pregnancy are needed to verify these findings.

Mild iodine deficiency during pregnancy is associated with reduced educational outcomes in the offspring: 9-year follow-up of the gestational iodine cohort

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Background: Iodine is an important micronutrient for normal fetal and childhood neurocognitive development. The few studies that have examined maternal iodine deficiency during pregnancy in relation to offspring cognitive development have found mixed results. The purpose of this study
was to examine the impact of maternal iodine deficiency on educational outcomes of the offspring at 9 years of age.

**Methods:** This was a follow-up study assessing the impact of iodine deficiency during pregnancy. Maternal iodine deficiency was defined as a urinary iodine concentration <150 μg/l diagnosed anytime during pregnancy and treated. Educational outcomes were measured and included Australian and Tasmanian standardized educational tests that assess spelling, grammar, English literacy, reading, writing and mathematics/numeracy.

**Results:** Follow-up data was available for 228 children. In unadjusted analysis, offspring of mothers with iodine deficiency had lower spelling, grammar and English literacy scores compared to offspring of women who were iodine-sufficient. However, after adjusting for biological and socioeconomic factors, only spelling scores remained significant. Offspring of iodine-deficient mothers had a 38.6-point reduction (95% CI –65.6 to –11.6; p = 0.005) in spelling scores when compared to offspring not exposed to iodine deficiency.

**Conclusion:** These results suggest exposure to gestational iodine deficiency has long-term cognitive effects even when iodine insufficiency is corrected during childhood.

**Comments**

Only one report of iron-deficiency anemia (IDA) and cognition was published this year. Algarin et al. studied a group of 10-year-old Chileans diagnosed with IDA and treated during infancy and compared them to a group without IDA. Even though treated for IDA in infancy, IDA during infancy was linked to cognitive and electrophysiological impairment at 10 years of age.

The effects of perinatal vitamin A supplementation on cognitive development in 10- to 13-year-old children were evaluated in a cohort from rural Nepal. No differences were found on non-verbal IQ and motor ability using standardized tests between children in the villages randomized to provide vitamin A to women of reproductive age and villages not randomized to vitamin A. The only difference found was that fewer children had to repeat a grade in school if they were born in a village given treatment. Given the importance of good vitamin A status for immune function, it would have been helpful to have information on missed school days to determine if this finding was related to a cognitive effect or that the children were simply healthier and better able to attend school.

The role of iodine status during pregnancy was evaluated in two studies this year – one conducted in the UK ALSPAC cohort and one conducted in Australia and Tasmania. Both found adverse effects on cognitive function of offspring of women with iodine deficiency during pregnancy (characterized as a urinary iodine of <150 g/μg of creatinine or <150 μg/l for these respective studies). IQ was determined with the WISC in the ALSPAC cohort when children were 8 years of age; a test of writing ability was conducted at 9 years of age. Verbal IQ, reading accuracy and reading comprehension were more likely to be in the lowest quartile for offspring of iodine-deficient mothers. The Australian and Tasmanian cohort were tested on standardized education tests with only spelling scores significantly lower in offspring of iodine-deficient compared to iodine-sufficient women at 9 years of age.

**Overall Summary:** The majority of the studies published this year used well-established cognitive assessments or assessments targeted to specific behavioral domains and were done at ages when the assessments could be used to discriminate between children's performance (tests were age-appropriate, but not too easy or too difficult). Many also used multiple measures of cognitive function and tested children at school age when cognition is better measured. It is also heartening that most controlled for potentially influential variables to minimize the chances that findings were due to other forms of deprivation. The studies for the most part studied large cohorts and appear to be
adequately powered to accept or reject the null hypothesis. These are all signs of increasing sophistication in studies of nutrition and cognitive development compared to the past, and they suggest productive collaboration between nutrition and developmental scientists. The overall impression left by studies published this year is that many nutrient deficiencies early in development can lead to adverse effects on cognitive development at school age. However, it is clear that some of these studies have only opened the door. More studies are needed to provide the quality of evidence needed to create public policy.