
Cognition

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This chapter collects the articles that have been published between the dates July 1, 2013 and June 30, 2015 in the area of cognition and nutrition. All studies were human observational or clinical trials, or systematic reviews.

The topic of the relations between nutrition and cognition is slowly expanding from the parental associations between breastfeeding and development. From the first trials which included very significant breastmilk components such as long-chain polyunsaturated fatty acids, now other nutrients are being included (e.g. the role of breakfast and selected micronutrients, but always keeping human milk and breastfeeding as central areas), and the sensitive period goes back to pregnancy and extends through childhood (see the questions of breakfast and glycemic load). Indeed, our societies, which are both well developed and at the same time very fragile, require not only the optimal development of brain structure and functioning of infants and children, but also their rapid adaptation in day-to-day activities, at school and in their professions when they become adults.

A second reason for this expanding body of research is represented by the run up towards nutritional claims that are progressively emerging among stakeholders following the normative issues, which (for example) in Europe has led to the creation of the EFSA (European Food Safety Authority). Accordingly, a nutrition claim as well as an opinion on a food constituent, presumably benefitting either producers in terms of income or consumers in terms of health, needs a sound body of evidence to get approval. Since the improvement of mental performance is universally considered a beneficial effect, more randomized controlled trials and reviews in this field have taken place and are also expected in the coming years.

Accordingly, the articles included here fall into 1 of 4 categories: pregnancy and breastfeeding, long-chain polyunsaturated fatty acid supplementation, micronutrients (iodine, iron and vitamin B), and glycemic load and glycemic index. Overall commentaries are included for each section following the summaries of papers and respective commentaries within each category.

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Breastfeeding and trajectories of children's cognitive development

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Background: It is widely agreed upon that breastfeeding is associated with increased cognitive development, but the mechanism by which breastfeeding improves cognition is a matter of debate. This study examined the relationship between breastfeeding and the growth trajectories of children's cognitive ability over time using longitudinal data.

Methods: The authors used data from three waves of the Child Development Supplement (CDS) of the Panel Study of Income Dynamics (PSID). Children who had at least one valid measure on standardized achievement tests among three waves (1997, 2002 and 2007 if they were still younger at the interview) and had valid information on breastfeeding were included ($n = 3,129$ with a range of age of 3–17 years). Tests have been used to evaluate children's reading and math ability [letter-word identification (LW) test; applied problems (AP) test; passage comprehension (PC) test]. Three major independent variables were used: children's age, a dichotomous indicator on whether children were breastfed and a continuous variable of the duration of breastfeeding.

Results: After limiting the study to subjects living with biological mothers and having parents in their households ($n = 2,784$), the few children with missing values were also excluded; the final sample size was 2,681. About 60% of the sampled children were breastfed, and the average duration of breastfeeding was 3.4 months. More than 60% of subjects were White children, and half of the children were male. For the AP, LW and PC tests, there was a slight upward trend in early childhood, and a slight downward trend was noticed in late childhood. The coefficients of child's age and age squared were only significant at the 0.1 level in the analysis of the PC score. The results showed a positive association between breastfeeding and children's cognitive ability in early childhood, but did not correlate with the growth rate of cognitive ability. A 1-month increase in the duration of breastfeeding raised the AP, LW and PC scores, respectively, by 0.4 points (95% CI: 0.10, 0.69; $p < 0.01$), 0.4 points (95% CI: 0.12, 0.72; $p < 0.01$) and 0.2 points (95% CI: -0.03, 0.46; $p < 0.10$). Since the mean duration of breastfeeding was 3.4 months, these estimations suggest a weaker association between breastfeeding and test scores (LW, AP and PC tests).

Conclusion: The study makes unique contributions to the topic by examining the impact of breastfeeding practices on the growth trajectories of children's cognitive development. The effect of breastfeeding observed in the literature may reflect the 'true' effect of breastfeeding practices, rather than serving as a proxy for parental characteristics or other environmental factors. In this study, a consistent but weaker association between the duration of breastfeeding and test scores has also been estimated.

Comments Huang et al. point out that the effects of breastfeeding, after being present in early childhood, do not increase or dissipate over time. Indeed, the study is original in that it follows the neurocognitive achievements of breastfed versus formula-fed infants through all the pediatric ages, accounting for variables of interest. Even though the authors seem convincing in their conclusion that 'This indicates that we can be fairly

certain that a genuine breastfeeding effect exists, rather than breastfeeding being an indicator of unobserved variables (such as maternal nurturing) that have a contemporaneous effect on breastfeeding', we know that in other reviews as well as original works the positive breastfeeding effect still disappeared after accounting for variables. However, in support, a Danish paper [1] found positive effects of being breastfed and breastfeeding duration at 18 and 27 years of age, independent of a wide range of possible confounding factors. Should the 'pure' effect of breastmilk and breastfeeding appear later on, the high probability of collinearity with other variables should in any case always be considered.

The effects of breastfeeding exclusivity on early childhood outcomes

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Background: Most studies on the consequences of breastfeeding have analyzed the association of breastfeeding (yes or no) with the main qualitative differences concerning aspects such as duration, exclusivity, volume and follow-up time points. Other studies with different outcomes were heterogeneous in study designs and the type of outcome, and even the only semirandomized study design could not be blinded.

Methods: The authors used a large representative study cohort of 10,700 children born in the United States in 2001 (the Early Childhood Longitudinal Study – Birth Cohort) with detailed infant feeding data. These data included parent interviews and child assessments with the focus on health and cognitive outcomes at ages 2 and 4 years. Interviews were conducted in measurement waves at 9 months, 2 years, 4 years and in kindergarten. These outcomes were measured using indicators of child well-being in terms of health and cognition. Outcomes at 2 years included cognitive and motor skill scores and BMI, while outcomes at 4 years included scores for math, reading, fine motor skills and BMI. Data were analyzed through the propensity score methodology. This method has several potential advantages over standard regression, which are primarily diagnostic and include checking covariate balance.

Results: At 2 years of age, the results indicated no dose-response pattern of breastfeeding on mental ability, a small association between breastfeeding and motor ability, and no significant effects of breastfeeding on BMI. At 4 years of age, the effects of breastfeeding on reading, math and fine motor skills were positive and ranged from small to medium effect sizes, with no associations with dosage.

Conclusions: Results of this study suggested some small but inconsistent effects of exclusive breastfeeding on key outcomes for children at ages 2 and 4 years.

Comments The report of Jenkins and Foster is the negative mirror of the previous survey. Taking the opportunity of a similar setting, the results from progressive assessments of children at 2 and 4 years, neither direct effects nor dose-related effects were found. According to the authors, the statistical methodology used may allow for a better balance of covariates, partly reducing the bias of nonrandomized, nonblinded trials. It cannot be concluded as to which is right; however, both of these studies, mainly for the reason of being similar but diverging in conclusions, suggest to be prudent on the conclusions concerning breastfeeding effects.

Infant feeding effects on early neurocognitive development in Asian children

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Background: A good deal of research has investigated the association between breastfeeding and cognitive performance, but few well-controlled studies have examined the potential benefits of breastfeeding on specific cognitive processes within the first 2 years of life. In this article, the authors report a study that assesses the relation between infant feeding and cognitive development among healthy children in Singapore of Chinese, Malay and Indian ethnicity at 6, 18 and 24 months of age.

Methods: 408 participants took part in the neurocognitive assessments at 6, 18 and 24 months. For this analysis, subjects whose mothers had pregnancy complications were excluded. Interviewers administered feeding practice questionnaires to mothers. The mothers were subjected to interviews at 3 weeks, 3 months and 6 months postpartum to classify the type of feeding (exclusive, predominant, partial or no breastfeeding), and were also asked when they stopped breastfeeding and when they introduced solid food to their infants. Infants were defined as having high, low or intermediate breastfeeding according to the type and duration of breastfeeding. Neurocognitive tests included memory and attention tasks.

Results: Breastfeeding was associated with better performance in only 4 of 15 cognitive measures. In 6-month-old infants, high-breastfeeding infants tended to recall more target behaviors than did low-breastfeeding infants. At 24 months of age, toddlers were able to reproduce comparable numbers of target behaviors across the breastfeeding groups. This difference was statistically significant only for the intermediate-breastfeeding group. At 24 months, toddlers with longer breastfeeding duration were able to recall more target behaviors in the correct sequence (p trend = 0.009). A positive association was observed between the high-breastfeeding group and language domain scores. The scores in cognition and motor (fine and gross) domains were comparable across the groups. Similarly, a secondary analysis showed that higher scores in receptive (p trend = 0.001) and expressive (p trend = 0.002) language domains were associated with longer breastfeeding duration.

Conclusions: Intensive neurocognitive testing of Asian children in the first 2 years of life suggests a significant, albeit modest, beneficial effect of breastfeeding on young children's memory and language development.

Comments This study, pioneering in the context of Asian children, looks at different domains of brain function associated with breastfeeding and beyond the main developmental milestones of the first year of life. The results are a sort of compromise with the previous two studies. The follow-up is further limited to 2 years (so relatively in the short-medium term), and the associations are numerically limited to 4 out of 15 tests. The analysis utilized the regression methodology with adjustment for covariates. Therefore, the heterogeneity characterizing the scientific literature on human milk and breastfeeding is still clear and well represented. The consistency of the identified effects (i.e. memory and language) with the results from other reports may counteract the justified suspects of some chance findings, in consideration of the high number of tests that were performed.

Supplemental feeding during pregnancy compared with maternal supplementation during lactation does not affect schooling and cognitive development through late adolescence

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Am J Clin Nutr 2014;99:122–129

Background: While there is extensive evidence that nutrition affects cognitive capacity of children, inadequate maternal nutrition is also a recognized risk factor in child development. A randomized trial in Guatemala showed a weak evidence base for long-term effects of macronutrient supplementation. The current study tested the hypothetical beneficial effects of a nutritional supplementation during pregnancy and lactation on the cognitive ability of the offspring as young adults.

Methods: Children whose mothers were provided nutritional supplements in a randomized trial in the West Kiang region of Gambia between 1989 and 1994 took part in the study. According to the original study design, all the pregnant women from 28 villages were assigned to a group who received either two protein-energy-fortified biscuits/day from 20 weeks of gestation to delivery or a control group who received the biscuits for 20 weeks postpartum. The current study tracked all individuals who were born during the original study, whether or not they were interviewed in 2005 and 2006. The sample ranged from 16 to 22 years of age at the time of follow-up and tests were used to assess cognitive abilities (Raven's, Mill Hill and digit-span test). Anthropometric measurements were also made.

Results: A follow-up sample of 1,459 children was available for the investigation, out of the 2,047 live births in the original trial. The mean age at follow-up was 19 years, and 50.1% of the recruited sample were boys. There were no major differences in cognition or education between subjects whose mothers received the treatment during pregnancy and subjects whose mothers received nutrition during lactation.

Conclusions: This study found no sustained effect of a protein-energy supplementation of women during pregnancy or during lactation on the cognitive ability and school performance of offspring.

Comments The study evaluated the effects of maternal supplemental feeding on cognitive ability within a typical African setting, represented by Gambia. The expected improvement in cognitive ability of children whose mother received supplementation (energy and proteins) during pregnancy or in lactation did not take place. This result was explained by the authors in several ways, from the lack of sufficient power to detect differences up to inadequate methodology or imbalances in the complex branches of the original study design.

Overall Commentary

The four studies taken together provide a good opportunity to assess the status of the literature on human milk and breastfeeding associations, as well as supplementations in pregnancy, with cognitive performance, and highlight the major points to be addressed in future studies. The significant heterogeneity in study designs still precluded the conduct of a formal and rigorous meta-analysis. As a consequence, it is difficult to counteract the hypothesis that much of the reported effect of breastfeeding on child neurodevelopment could be due to confounders, e.g. maternal intellectual and socioeconomic effects. It is likely that additional studies could change the current synthesis if conducted with the attempt to rigorously control for all important confounders, or using sound and/or new methodologies of statistical analysis, considering that randomized trials with breastfeeding are simply impossible. According to another suggested alternative, study designs might yield more robust conclusions by including sibling cohorts discordant for breastfeeding [2]. Finally, the effects in pregnancy from the popular long-chain polyunsaturated fatty acid supplementations are quite limited. In any case, effects are expected from maternal supplementations in conditions that are at risk of unbalanced diets, in spite of the negative results in the trial reported here.

Long-Chain Polyunsaturated Fatty Acids

Effects of long-chain PUFA supplementation in infant formula on cognitive function in later childhood

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Am J Clin Nutr 2013;98:536–542

Background: Long-chain polyunsaturated fatty acids (LC-PUFAs) are essential for normal brain development. An unclear question is whether the influence of LC-PUFAs on cognitive function is confined to the period of infancy or continues into later childhood. The aim of this study was to define the effect of LC-PUFA supplementation in infant formula on cognitive ability in children at 6 years of age.

Methods: In this study, a cohort of children randomly received two trial formulas during the first 4 months of life; one containing LC-PUFAs and another one without LC-PUFAs. The infant formulas were commercially available and were identical apart from the addition of docosahexaenoic acid and arachidonic acid to the LC-PUFA formula and small adjustments. Children and their families were invited to attend a clinic in each study center when the children were aged 6 years \pm 2 months; during these visits, interviewers administered cognitive tests and questionnaires to children and their parents. In particular, the cognitive performance of the children was assessed with the Wechsler Preschool and Primary Scale of Intelligence-Revised (WPPSI-R), the Day-Night Test, and the Matching Familiar Figures Test (MFFT), which provided standardized IQ scores, performance IQ (PIQ), verbal IQ (VIQ) and an overall full-scale IQ score (FSIQ) and measured the ability to control attention and ignore irrelevant and distracting information. These are all measures of impulsivity and efficiency at processing information.

Results: 235 of the 376 children in the original trial took part in this study: 71 in the LC-PUFA group, 76 in the non-LC-PUFA group and 88 in the reference breastfed group. The mean age of the children at the time of assessment was 70.1 ± 3.5 months. WPPSI-R scores showed no significant differences between the two formula groups on PIQ, VIQ and FSIQ. Performance on the Day-Night Test did not differ between the two formula groups. There were no differences between the randomized formula groups in the number of MFFT errors, but the LC-PUFA group had significantly lower MFFT efficiency scores, with lower scores indicating more efficient processing [$F(1, 132) = 4.66, p = 0.033$].

Conclusions: The authors found no significant differences between the two groups on any IQ measure and no evidence that LC-PUFAs in infancy influenced the development of attention control at 6 years of age. LC-PUFAs in infant formula had no effect on children's ability to solve the MFFT problems, but response latencies on the MFFT were shorter in 6-year-old children who were fed a formula containing LC-PUFAs; these formulas were associated with improved speed of information processing.

Comments The debate on the measurable effects of LC-PUFA supplements at early age to either preterm or term infants is more than open, as shown by the very high number of studies and trials as well as the uncertainties of the messages at the end of systematic reviews and Cochrane documents. The heterogeneity of study designs, the lack of knowledge on the baseline status of LC-PUFAs before the trial and the recent overflow on the roles of desaturase haplotypes represent factors that could allow for more firm conclusions only when assessed together. Nevertheless, the assessment of possible long-term functional effects may be suggestive, at this stage, of further hypotheses. These results suggest that the effects of LC-PUFAs on speed of information processing are not transient but persist beyond infancy. These differences could depend on effects on visual acuity (since the MFFT is a visual test) or speed of processing at a superior brain level.

Effects of maternal omega-3 supplementation on fatty acids and on visual and cognitive development: a randomized trial

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J Pediatr Gastroenterol Nutr 2015;61:472–480

Background: Docosahexaenoic acid (DHA) has putative effects related to visual function and to central nervous system development. It is important to obtain the maximum information about the lipid profiles in both mothers and newborns. The aim of this study was to evaluate the role of a dairy drink supplemented with omega-3 LC-PUFA taken by mothers during pregnancy and lactation on the lipid profile of the mother and the newborn, and to evaluate the possible influence of fish oil supplementation on visual and cognitive development.

Methods: 110 volunteers, who were recruited between June 2009 and August 2010 from two hospitals, took part in this randomized control trial. The dietetic intervention began in the 28th week of pregnancy and finished in the fourth month of lactation. The mothers were randomly assigned to one of two intervention groups: control group (CT) = 400 ml/day of the control dairy drink, and fish oil group (FO) = 400 ml/day of fish oil-enriched dairy drink. Mother's dietary intake, especially the n-3 LC-PUFA consumption, was assessed using a validated 110-item food frequency questionnaire (FFQ), a 72-hour diet record and information about food and physical activity habits. Blood fatty acid profiles were determined in blood samples that were collected from mothers and from all neonates at the moment of enrollment, at delivery, at 2.5 months postpartum and at the end of the dietary intervention; the profiles were also measured in the placenta and breast milk. To evaluate visual function, binocular visual evoked potentials were obtained in 60 healthy subjects and in 53 infants, respectively, at 2.5 and at 7.5 months. Results from Bayley's test (at 12 months) were recorded to analyze cognitive abilities.

Results: This trial showed no statistically significant differences in age, height, weight and biochemical parameters in the anthropometric parameters and in the maternal nutritional intake between the two groups. The DHA percentage in plasma, erythrocyte membranes and breastmilk samples was significantly higher in the FO group compared to those of the CT group. The percentage of nervonic acid was significantly higher in mothers of the FO group at delivery and at 4 months, and also in plasma and erythrocytes from neonates of the FO group. No differences were seen in visual evoked potentials and Bayley's tests between the two intervention groups.

Conclusions: The authors showed the important influence of dairy drinks supplemented with omega-3 LC-PUFA taken by mothers during pregnancy and the lactation period on the fatty acid profile and the nervonic acid content of the mother and the newborn. However, maternal supplementation with omega-3 LC-PUFA had no influence on visual function and no neurodevelopment effects in this study.

Comments This study is interesting because it considers new aspects: effects of LC-PUFA supplements on mothers already on a balanced diet, the attention to nervonic acid levels (whose role in the very early ages is debated as far as functional roles), blood sampling for fatty acids at different time points and functional outcome with the visual evoked potentials. Although the study is sufficiently powered, only expected biochemical changes were seen in the DHA levels and only minimal differences were seen with the visual evoked potentials, leading the authors to conclude that there were no effects on visual and cognitive/psychomotor development. When calculating the power of the test, future studies should perhaps include a sufficient number of infants to check gender-related differences and (if possible) the effects of FADS haplotype polymorphisms.

Randomized controlled trial of maternal omega-3 long-chain PUFA supplementation during pregnancy and early childhood development of attention, working memory, and inhibitory control

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Background: During the last trimester of pregnancy, omega-3 long-chain PUFA docosahexaenoic acid (DHA) accumulates in neural tissues at a great velocity. These areas of the brain are responsible for higher-order cognitive skills known as executive functions (EFs). This is the first study to compare early childhood EFs after maternal supplementation with DHA or a placebo during pregnancy.

Methods: 185 children born to mothers enrolled in a double-blind randomized controlled trial took part in the current study. The mothers were randomly assigned to one of two intervention groups: treatment-group women were asked to consume three 0.5-gram DHA-rich capsules/day, which provided 800 mg of DHA/day and 100 mg of eicosapentaenoic acid/day from enrollment until delivery, and control-group women were asked to consume three 0.5-gram capsules that contained a blend of vegetable oils. The study excluded children who were born preterm, had low birth weight, or had neurologic or visual pathologies. At a mean age of 27 ± 2 months, the children were submitted to measures of attention by using three attention tasks: single-object (SO) task, multiple-object (MO) task and distractibility task. An attention and working memory and inhibitory control (WMIC) task was used to assess WMIC; the test proceeded in 5 consecutive phases: learning trials, training trials set 1, test trials set 1, training trials set 2 and test trials set 2. Cord blood was collected and plasma phospholipids were analyzed.

Results: 184 children were eligible to participate in the study. 81 children in the treatment group and 77 in the control group took part in the assessments. The outcome of the distractibility and the SO and MO tasks did not differ between the treatment and control groups. There was one exception: the number of times children looked away from the toys in the MO task was lower in the treatment group than in the control group, although the difference was weak. The primary outcome of the WMIC task did not differ between the two groups. The control group was more accurate at

searching for the hidden toy during training trials. Cord blood samples were collected from 66 treatment-group participants and 60 control-group participants, and the results showed an overlap of cord plasma DHA between groups. However, associations between plasma DHA with attention and WMIC outcomes were inconsistent.

Conclusions: There was no positive association between DHA supplementation and attention and WMIC. Future research is needed to determine whether supplementation of specific populations, such as those born preterm, is of benefit to their cognitive development.

Comments Due to the usual overflow of positive associations and results from smaller trials, this study which showed no functional effects on infants/children at medium term (27 months) is welcome and indicates the need to explore more in depth the effects of omega-3 LC-PUFA supplementations in some 'at risk' categories, such as premature infants.

Maternal LC-PUFA status during pregnancy and child problem behavior: the Generation R Study

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Background: Long-chain polyunsaturated fatty acids (LC-PUFAs) play an important role in brain function and development. Because of this role, LC-PUFA status, either measured in cord blood or maternal blood, during gestation has been hypothesized to affect the risk of problem behavior in children. The aim of this study was to test the hypothetical association between maternal LC-PUFA and child emotional and behavioral problems at 6 years of age.

Methods: The present study was conducted within the Generation R Study. 8,663 women took part in the study before their third trimester of pregnancy, and valid fatty acid profiles in plasma were available for 6,999 mothers. One measure of child behavior was available for 5,307 children and their mothers. The authors measured maternal plasma docosahexaenoic acid (DHA), eicosapentaenoic acid (EPA), and arachidonic acid (AA) concentrations and n-3:n-6 ratio in midpregnancy. Child emotional and behavioral problems at 6 years of age were assessed.

Results: The authors found indications of higher maternal DHA levels and n-3:n-6 ratio during second trimester of pregnancy to be associated with fewer emotional problems, and higher AA levels with more behavioral problems in the offspring at the age of 6 years, using teacher and combined parent/teacher scores. No associations were found between maternal EPA and child behavioral problems.

Conclusion: Further studies should be carried out to identify LC-PUFA-sensitive periods of fetal brain development, optimal intake of LC-PUFAs during pregnancy, and the specific effects of inadequate prenatal LC-PUFA status on emotional and behavioral development in the offspring.

Comments After a negative randomized controlled trial on maternal supplementation in pregnancy, here is a cross-sectional study indicating major risks of affective and behavioral problems at 6 years of life for children born to mothers with lower n-3 LC-PUFA and higher n-6. So the question arises, how would it be possible again to identify mothers mostly benefitting from higher n-3 supplementation in pregnancy?

Overall Commentary

The research on the functional effects of LC-PUFA is moving towards considering functional effects at higher ages, and particularly focusing on the maternal supplementation in pregnancy or lactation. Maybe we are moving towards a second era of research, with less heterogeneity of study designs, higher statistical power and more predefined methodology inclusive of genes and gender. In the meantime we still must accept the heterogeneity of results paralleling the heterogeneity of study designs. As repeatedly mentioned within the single comments to individual studies, ideal designs of LC-PUFA effect in brain functions should include: (1) assessment of the fatty acid status at least at baseline and at the end of the trial period, (2) administration of homogeneous developmental tests to allow for between-study comparisons, (3) statistical power sufficient to check the gender-related effects and (4) adjustment for the desaturase haplotypes, then a sample obtained for this specific aim.

Micronutrients

Effect of iodine supplementation in pregnancy on child development and other clinical outcomes: a systematic review of randomized controlled trials

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Background: Iodine is essential for normal growth and development. Severe iodine deficiency in pregnancy causes cretinism and brain damage in infants. This study evaluated the relation between iodine supplementation with growth and development of children, with pregnancy and other clinical outcomes and with iodine status and thyroid function.

Methods: The authors conducted a systematic review of randomized controlled trials with PubMed, MEDLINE, EMBASE, CINAHL, Psyc-INFO and Cochrane Central Register of Controlled Trials. They compared the effects of iodine supplementation with a parallel control group who received no iodine supplementation, during pregnancy or the preconceptional period, on outcomes in all participants and their offspring. Women were randomly assigned to receive either iodine or placebo supplements daily from trial entry to delivery, or into the postpartum period.

Results: A total of 14 publications were included in the review. Trials were conducted in rural settings in areas of severe iodine deficiency and in regions of mild to moderate iodine deficiency. Studies in regions of severe iodine deficiency were considered. In a trial from Peru, no differences be-

tween iodine and placebo groups were reported for the growth and development outcomes. Birth weight, length, head circumference, placental weight or Apgar scores at birth and child mortality did not differ between two groups. In a subgroup analysis, no differences between groups were reported for growth rate, skinfold thicknesses and postnatal bone maturation up to 5 years of age between the two groups. In a trial from Papua New Guinea, the incidence of cretinism in the 27 villages originally randomly assigned was 2% in the iodine group compared with 6% in the placebo group. As far as studies in regions of mild to moderate iodine deficiency, none of the trials reported outcomes related to the growth, development of children or pregnancy. Iodine supplementation led to increases in both maternal and infant urinary iodine excretions as well as iodine concentrations in breast milk when assessed, but no clear dose-response relation was seen.

Conclusions: No evidence regarding the effect of iodine supplementation in pregnancy on growth and development of children was observed, but the leading health authorities recommended routine iodine supplementation in pregnancy. Before giving any advice, it should be considered that iodine supplementation in pregnancy may not be without risk because of the safe upper limit in pregnancy is uncertain.

Comments The issue of micronutrients extends to all the issues involving human health, including cognitive development, and represents one of the hottest topics today. Indeed, the lack of data is impressive, leading institutional bodies to build an evidence based on few reports in order to get reliable AR and/or PRI values of reference for any given micronutrient. The review mentioned here failed to find measurable effects on infant development from iodine supplementation in pregnancy. In spite of the present recommendations, the issue is still open, and future trials should also carefully evaluate the safety issues, considering also the studies reporting some negative effects. These results are in contrast with an important, recent, observational study [3] that has already been commented on in the previous edition of this review [4]. Accordingly, suboptimal iodine levels in pregnancy were found to be associated with lower developmental and cognitive outcome measures at 8 years. The history of the science behind the major macronutrients (even iron, for instance) has a common denominator: observational associations with cognitive function and development in spite of few (if any) substantiation from randomized trials. Maybe a rethinking of the most adapted methodological approach in this area could be welcome.

The effects of regular consumption of a multiple micronutrient fortified milk beverage on the micronutrient status of school children and on their mental and physical performance

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Background: Multiple, concurrent micronutrient deficiencies exists in young school children in low-income countries. Iron deficiency anemia (IDA) is a major public health problem in India. In addition to iron deficiency, others deficiencies are seen with vitamin A, iodine, B vitamins and zinc;

the suboptimal supply of the micronutrients could affect the functional and neurobehavioral development of the children. The objective of this study was primarily to assess the effect of a multi-micronutrient fortified milk beverage as compared to an energy matched nonfortified milk-based drink on the micronutrient status of children aged 7–10 years, and the effect of the multimicronutrient fortified milk beverage on cognition, physical performance and nutritional deficiencies.

Methods: 227 children took part in this randomized, double blind, placebo-controlled study. This study included two parallel groups (control and intervention): children received randomly two trial drinks – one multimicronutrient fortified drink and another unfortified isocaloric drink. The drink was served twice daily, 6 days a week for a period of 5 months. Anthropometric measurements were carried out. Blood samples have been collected for biochemical analyses. The dietary intake of each child was assessed using a 3-day dietary recall method. Assessment of morbidity was evaluated using questionnaires, and physical performance was evaluated using standardized tests. Cognitive tests assessed the broad domains of attention (mental alertness), short-term memory and executive functions (working memory, planning, cognitive flexibility, creativity).

Results: Of the 227 children who were enrolled, 224 completed the study. The mean age of the children was 8.2 ± 0.9 years, and 77% of them were girls. The dietary intake of the children was comparable between the study groups. The mean change in height of the children in the control and intervention groups at the end of the study showed a trend toward significance, with a better effect observed in the intervention group ($p = 0.07$). Levels of vitamin B₁₂, red cell folate and vitamin B₂ were significantly higher in the intervention group ($p < 0.001$). Vitamin D, selenium levels and body iron did not differ between the two groups at the end of the study. The prevalence of vitamin B₂ deficiency was also significantly lower in the intervention group as compared to the control group ($p < 0.001$). At endline, there was an improvement in the physical endurance and agility in both the groups with no significant interaction between the study groups with time and status. The endline cognitive performance was significantly greater than that at baseline for both the study groups, without any significant interaction effect between the study group and time/status.

Conclusions: The micronutrient fortified drink had a beneficial effect on the status of vitamin B₁₂, vitamin B₂ and red cell folate levels. The intervention group children were able to maintain their Hb levels during the study period and showed a slight though not statistically significant improvement in their serum ferritin levels at the end of the study. The results of this study show that a micronutrient fortified milk-based drink reduces the risk of deficiencies of certain micronutrients (iron, anemia, vitamin B₁₂) in apparently healthy children from lower to middle socioeconomic groups.

Comments The debate on the effects of special milks for young children has generated a wide debate in Europe since, in the face of potential benefits deriving from their composition on the dietary balance, the body of evidence supporting their use is small [5]. The question may be different for developing and transition countries, where the major point is not balance but a sufficient supply to counteract nutritional deficiencies, particularly micronutrients whose effects on brain development and mental performance are recognized from observational studies. Accordingly, these special milks could be consumed daily through all pediatric ages. In the present study, the biochemical status of supplemented children improved, while the overall developmental stages were similar in the two groups. It is also likely that major effects should be expected with the selection of more disadvantaged groups that could benefit from supplementation. Associations with specific and more sensitive genetic patterns are still a matter of basic research.

Three-month B vitamin supplementation in pre-school children affects folate status and homocysteine, but not cognitive performance

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Background: Poor intake of dietary vitamins B₂, B₆, B₁₂ and folate leads to several problems in cognitive development and neurological abnormalities. The aim of this study was to test the hypothesis that short-term (3 months) dietary supplementation with folic acid and vitamins B₁₂, B₆ and B₂ improves folate status, decreases homocysteine and affects measures of cognitive performance in healthy preschool children.

Methods: 250 healthy children aged 4–6 years were recruited for this randomized controlled trial and randomly assigned to one of the intervention groups. The intervention product was provided as a flavorless powder in sachets containing folic acid (220 µg), riboflavin (1.1 mg), pyridoxine (0.73 mg), cobalamin (1.2 µg) and calcium lactate pentahydrate (130 mg). The control matched the intervention product in taste and appearance, but contained only 130 mg calcium. Subjects received either the intervention or the control product over a period of 90 days at home. Families were asked to complete questionnaires on socioeconomic, demographical and food frequency information, and a battery of cognitive tests was administered to all participating subjects before and after the intervention. Urine was collected at home and aliquots were stored at –80°C until analysis of methylmalonic acid (MMA), acetyl-para-aminobenzoyl-glutamate (ap-ABG), and folate and vitamin B₁₂ status.

Results: The participating children had a mean age of 5.5 years; postintervention assessments of cognitive performance were completed by 115 children in the intervention group and 122 children in the control group. Compared to controls, at the end of the 3-month intervention, median whole blood folate was about 50% higher ($p < 0.0001$) and ap-ABG was 4 nmol/mmol higher in the vitamin B- and folate-receiving group ($p < 0.0001$), respectively. Homocysteine decreased by 1.1 µmol/l compared to baseline. We found no relevant differences between the groups for the cognitive measures before or after intervention.

Conclusions: This study did not find any indication of an effect on cognitive function of vitamin B and acid folic supplementation for 3 months in healthy preschool children.

Comments In spite of a few positive findings, particularly in the elderly, this randomized controlled trial did not find any indication of an effect on cognitive function of vitamin B supplementation for 3 months in healthy preschool children, despite a marked change in folic acid, homocysteine, ap-ABG and vitamin B₁₂ status. The authors explain that the participating children lived mostly in above-average conditions in terms of housing and parental income. As is the case of the observations from previous surveys, it is likely that effects might be mostly found in subgroups with suboptimal levels at the start of the trial, perhaps arising from either disease- or gene-related conditions.

Overall Commentary

Micronutrients (iron, iodine, group B vitamins, etc.) have a defined role in the brain at the functional level, entering the cycles of coenzymes. Yet, in spite of convincing observational reports on associations with functional activities, randomized trials rarely describe effects of supplementations, even when adequately powered. Heterogeneity in population responses has not been convincingly explored yet, and it is likely that a lot of work should be done in the future to disentangle who could benefit from supplemented micronutrients the most and how. On the other hand, the progressive recognition of homeostatic and preservative mechanisms suggest prudence in performing indiscriminate supplementations unless positive effects are clearly proven.

Glycemic Load and Glycemic Index

The effect of breakfast composition and energy contribution on cognitive and academic performance: a systematic review

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Background: In the past, many studies have investigated the influence of breakfast consumption on cognitive performance. The aim of the current systematic review is to collect existing evidence on the importance of nutrient composition or energy intake at breakfast, in absolute or relative terms, for cognitive and academic performance.

Methods: The authors carried out a literature search of PubMed to identify all the articles on the relation between cognitive, academic and school performance and breakfast composition and energy intake published in English up to November 22, 2013. Two authors independently selected the articles that were included or excluded according to specific criteria.

Results: The authors identified 102 articles, of which 83 remained when we limited our search to humans and to the English language. After the exclusion of articles that met the exclusion criteria, six additional articles were identified from manual searches of the reference lists of the selected original and review articles. Altogether, 15 articles were included in the systematic review. Of these, three provided information on the relation between cognitive and academic performance and energy intake at breakfast, 11 provided the same information for the macronutrient composition of breakfast and 1 provided both aspects of the problem. In the current review, most selected studies were based on multiple testing sessions for each cognitive test and treatment option.

Conclusions: The heterogeneity of studies is very high and does not allow for drawing firm conclusions. Weak evidence suggests that maintaining a flatter glycemic response after the consumption of breakfast may positively affect the cognitive performance. The hypothesis of improved, protracted performance with a breakfast providing 20% or more of the daily caloric energy still needs to be proved.

Comments The authors have reviewed the evidence on the role of breakfast composition and energy contribution for cognitive performance. The predominance of studies on children and adolescents reflects the evidence that these categories may be particularly vulnerable to the nutritional effects of breakfast, and, at the same time, how they may represent ideal targets for studies in the field, also considering stakeholders' interests. Breakfast consumption may provide a continuous supply of energy (and selected nutrients) to modulate the short-term metabolic responses to fasting conditions. It may also provide long-term effects, including an improved nutrient balance and distribution, which may positively affect brain activity and academic outcomes. At the conclusion of the revision, some evidence suggests that a lower postprandial glycemic response is beneficial to cognitive performance. However, it remains unclear whether this effect is specifically due to either the glycemic index or glycemic load solely, to both, or to other effects unrelated to glycemic response.

The effect of using isomaltulose (Palatinose™) to modulate the glycaemic properties of breakfast on the cognitive performance of children

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Background: Even if previous studies have focused attention on the glycemic properties of the meals in associations with cognitive functioning, it is unclear if the glycemic response rather than the macronutrient composition of the meal has a major role. The present objective was to consider in children the influence of isomaltulose provided in isocaloric meals with the same macronutrient composition, consumed in a dose-sufficient way to produce a significant difference in glycemic load (GL).

Methods: Seventy-five children, aged 5–11 years (average: 8 years 8 months), were recruited from four schools. Children attending a school breakfast club were recruited on 2 different days, at least 1 week apart, and ate one of two meals designed to differ in their GL: a meal sweetened with either isomaltulose (Palatinose™; GL 31.6) or glucose (GL 59.8), while keeping the macronutrient composition constant. Indeed isomaltulose, compared with sucrose or glucose, results in lower postprandial blood glucose and insulin responses over a prolonged period. The procedure was double-blind and the order in which the meals were consumed was randomly generated. Psychological testing took place 1 and 3 h after eating.

Results: Although the isomaltulose-based meal benefitted memory and mood regardless of the day on which it was consumed, there were also effects observed only on the second day of testing. On the second day, children processed information more quickly and had better spatial memory later in the morning after consuming the low-GL breakfast.

Conclusion: The lower-GL breakfast, which supplied isomaltulose, was associated with a slower decline in memory and attention throughout the morning. Although the explanation offered was a difference in the glycemic properties, the possibility cannot be excluded that there were other differences in the food items compared.

Comments Following the previous review paper, the study of Young and Benton tries to disentangle whether the glycemic response to a meal rather than its macronutrient composition carries a major role to support the cognitive function. The authors contrasted two breakfasts that offered identical levels of energy and macronutrients, although they differed in GL (just for a substitution with one component) – a study design rarely used. The lower-GL breakfast was associated with a slower decline in memory and attention throughout the morning. Starting on the second day of testing, children processed information more quickly and had better spatial memory later in the morning after consuming the low-GL breakfast. The benefits allowed for the conclusion that the glycemic nature of the meals was the underlying mechanism.

Dietary fiber is positively associated with cognitive control among prepubertal children

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Background: The role of diet on cognitive ability is still uncertain. This study evaluated the association between cognitive performance with prepubertal children's diet quality, fatty acids (FAs) and fiber intake

Methods: Sixty-five children took part in the study, aged between 7 and 9 years. A set of response inhibition tests (Flanker task) was used to evaluate the attentional inhibition. A 3-day food intake diary was submitted to children to assess the intake of nutrients obtained from the daily food consumption.

Results: Analysis showed that there was no association between task performance or diet measures and socioeconomic status and sex. Age, intelligence quotient, pubertal staging, maximal oxygen uptake and percentage of fat mass correlated with task accuracy. There was a positive association between congruent accuracy and insoluble fiber ($\beta = 0.26$, $p = 0.03$) and total dietary fiber ($\beta = 0.23$, $p = 0.05$). Incongruent response accuracy was positively associated with insoluble fiber ($\beta = 0.35$, $p < 0.01$), pectins ($\beta = 0.25$, $p = 0.04$) and total dietary fiber ($\beta = 0.32$, $p < 0.01$). Diet variables were not related significantly to reaction time measures.

Conclusion: The results of this study showed the positive effects of dietary intake, particularly dietary fiber, on cognitive control among prepubertal children.

Comments This was a simple cross-sectional study, adequately powered, which looked at the associations of many dietary compounds with measures of mental performance. It provides novel evidence relating dietary intakes to cognitive control among prepubertal children, particularly for total dietary fiber. Even if the authors mention another hypothesis on the link between dietary fiber, flora and brain activities, the effects of fiber on transit time, absorption and insulin response could represent (even alone) a plausible explanation of the observed effects.

Overall Commentary

The role of breakfast in younger age in balance energy intake and preventing overweight while supporting mental performance through the day has undergone a lot of observational studies and a few trials, as well as systematic reviews, in the last years. Once more, like the vast majority of nutritional studies, the heterogeneity of the study designs has limited conclusions. One possibility to reduce between-study heterogeneity is to identify single steps to change the single nutrient composition and to check the effects at different times. Within this context, glycemic index and/or glycemic load may be major determinants of brain function. Lastly, it would be opportune to separate the effects of breakfast itself as a main source of energy from the metabolic effects of its carbohydrate composition, on the cognitive performance.

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