Gestation and early childhood are crucial periods in child neurodevelopment and are critically dependent on several factors. Nutritional deficiencies may affect infant health, in particular brain development. Maternal nutritional status during pregnancy and breastfeeding and nutrients intake during infancy and childhood should be decided towards ensuring the genetic potential of brain growth and optimal functional outcomes through all the life-course. Several studies regarding the interaction of nutrients with neurocognitive performance of children have been performed. Available results are heterogeneous, while institutions are calling for newer evidence to substantiate recommendations on dietary intakes and/or specific nutrient integration. The microbial community represents the last promising frontier of the links between diet and development, and investigators are increasingly exploring this topic. Accordingly, a healthy commensal gut microbiota is crucial for a physiological neurocognitive development (but the definition of healthy is still under investigation, extending through the whole alimentary trait and beyond). New research should be devoted to understanding the patterns of gut microbial colonization and the mechanisms by which they may influence brain pathways.

This chapter comprehended a selection of recent articles including clinical trials, observational studies or reviews, in the area of nutrition and cognition. All articles have been selected from literature from July 1, 2016 to June 30, 2017 and fall into 4 categories: (1) long-chain polyunsaturated fatty acid (LCPUFA) gestation and lactation, (2) Micronutrients and neurodevelopment (3), Microbiome, and (4), a brief paragraph of Miscellanea. Papers have been summarized and comments are included following the summaries.
Key articles reviewed for this chapter

**LCPUFA**

**Long chain polyunsaturated fatty acid supplementation in infants born at term**
Jasani B, Simmer K, Patole SK, Rao SC
*Cochrane Database of Syst Rev* 2017;3:CD000376

**Prenatal supplementation with DHA improves attention at 5 y of age: a randomized controlled trial**

**Breastfeeding, polyunsaturated fatty acid levels in colostrum and child intelligence quotient at age 5–6 years**
*J Pediatr* 2017;183:43–50

**Association between maternal intake of n-6 to n-3 fatty acid ratio during pregnancy and infant neurodevelopment at 6 months of age: results of the MOCEH cohort study**
Kim H, Kim H, Lee E, Kim Y, Ha EH, Chang N
*Nutr J* 2017;16:23

**Docosahexaenoic acid and neurodevelopmental outcomes of term infants**
Meldrum S, Simmer K
*Ann Nutr Metab* 2016;69(suppl 1):23–28

**Impact of the n-6:n-3 long-chain PUFA ratio during pregnancy and lactation on offspring neurodevelopment: 5-year follow-up of a randomized controlled trial**
*Eur J Clin Nutr* 2017;71:1114–1120

**Micronutrients**

**Assessing infant cognitive development after prenatal iodine supplementation**
Bell MA, Ross AP, Goodman G
*Am J Clin Nutr* 2016;104(suppl):928S–934S

**Multiple biomarkers of maternal iron predict infant cognitive outcomes**
Thomas DG, Kennedy TS, Colaizzi J, Aubuchon-Endsley N, Grant S, Stoecker B, Duell E
*Dev Neuropsychol* 2017;42:146–159
Impact of maternal selenium status on infant outcome during the first 6 months of life
Varsi K, Bolann B, Torsvik I, Eik TC, Høl PJ, Bjørke-Monsen AL
Nutrients 2017;9:486

Maternal multiple micronutrient supplementation and other biomedical and socioenvironmental influences on children’s cognition at age 9–12 years in Indonesia: follow-up of the SUMMIT randomised trial
Lancet Glob Health 2017;5:e217–e228

Microbiome

Gut microbiota: a potential regulator of neurodevelopment
Tognini P
Front Cell Neurosci 2017;11:25

The central nervous system and the gut microbiome
Sharon G, Sampson TR, Geschwind DH, Mazmanian SK
Cell 2016;167:915–932

Miscellanea

Neurodevelopment: the impact of nutrition and inflammation during early to middle childhood in low-resource settings
John CC, Black MM, Nelson III CA
Pediatrics 2017;139(suppl 1):S59–S71

Assessment of neurodevelopment, nutrition, and inflammation from fetal life to adolescence in low-resource settings
Suchdev PS, Boivin MJ, Forsyth BW, Georgieff MK, Guerrant RL, Nelson III CA
Pediatrics 2017;139(suppl 1):S23–S37

Association between maternal nutritional status in pregnancy and offspring cognitive function during childhood and adolescence: a systematic review
Veena SR, Gale CR, Krishnaveni GV, Kehoe SH, Srinivasan K, Fall CH
BMC Pregnancy Childbirth 2016;16:220

Maternal dietary patterns during pregnancy and intelligence quotients in the offspring at 8 years of age: findings from the ALSPAC cohort
Matern Child Nutr 2018;14:e12431

Long chain polyunsaturated fatty acid supplementation in infants born at term
Jasani B1, Simmer K2, Patole SK3, Rao SC4
1King Edward Memorial Hospital for Women and Princess Margaret Hospital for Children, Subiaco, Australia; 2Neonatal Care Unit, King Edward Memorial Hospital for Women and Princess Margaret Hospital for Children, Subiaco, Australia; 3School of Paediatrics and Child Health, School of Women’s and Infants’ Health, University of Western Australia, King Edward Memorial Hospital, Perth, Australia; 4Centre for Neonatal Research and Education, King Edward Memorial Hospital for Women and Princess Margaret Hospital for Children, Perth, Western Australia, Australia
Cochrane Database of Syst Rev 2017;3:CD000376

This manuscript is also discussed in Chapter 3, pages 39–65.

Objectives: To assess the effectiveness and safety of LCPUFA supply on formula in full-term infants, focusing on neurodevelopment and physical growth.

Methods: Findings on the effect of LCPUFA supplementation in infants born at term on their cognitive function has been reviewed.

Main Results: Thirty-one RCTs were found and 15 of these have been included in the review (n = 1,889). All trials enrolled infants of ≥37 weeks’ gestation at birth. Recommendations as to whether infant formula should be supplemented with LCPUFA are controversial.

Conclusions: Conclusive findings on the impact of milk administration with LCPUFA in full-term infants are still lacking.

Comments
This Cochrane review included 15 RCTs that evaluated the safety and the effectiveness of supplementing formula with LCPUFA for visual acuity, neurodevelopmental outcomes, and physical growth in term infants. The overall quality of evidence was low and there is inconclusive evidence to support or refute LCPUFA supplementation of infant milk formula. For this reason, a recommendation of this common practice cannot be drown. A cost-benefit analysis on this issue becomes mandatory before concluding, as ever, “Well-conducted RCTs with adequate and reliable sample size are still needed.”
Prenatal supplementation with DHA improves attention at 5 y of age: a randomized controlled trial

Ramakrishnan U1, Gonzalez-Casanova I1, Schnaas L2, DiGirolamo A3, Quezada AD4, Pallo BC1, Hao W1, Neufeld LM5, Rivera JA4, Stein AD1, Martorell R1

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Am J Clin Nutr 2016;104:1075–1082

Background: Very few (if any) well-designed RCTs have assessed the influence of prenatal docosahexaenoic acid (DHA) supplementation on offspring brain growth and function at long term through childhood.

Methods: Neurodevelopment, behavioral and executive functioning, including attention have been assessed at 5 years of age in 797 children of Mexican women in a randomized controlled trial of prenatal DHA supplementation. In the present study 1,094 mothers were randomized to receive a total dose of 400 mg of DHA/day or a placebo from 18 to 22 weeks of gestation until birth. Measures of child cognition, behavior, and attention have been collected with the use of specific scales of intelligence and tests. Information about parental, environmental influence and social status have been assessed.

Results: No significant differences between intervention and control groups across a range of maternal and child characteristics have been found. Prenatal DHA supplementation had no overall impact on measures of cognitive functioning at 5 years of age, but interacted with the environmental effect on infant cognition in later life. Moreover, a potential effect of DHA supplementation during pregnancy on sustained attention in children at 5 years of age has been shown.

Conclusions: DHA supply in prenatal age may play a role in the development of global cognition, not limited with a better sustained attention in preschool children.

Comments

The objective of this randomized control trial was to define whether DHA supply during pregnancy improves child cognition and performance on an objective measure of attention at 5 years of age.

Results obtained in this study confirm this relationship and authors suggest that an adequate maternal DHA supplementation during gestation and breastfeeding represents the key to ensure optimal levels in children and consequently to obtain better outcomes, considering also the interactions with the environmental conditions. The long-term meaning remains to be interpreted.
Breastfeeding, polyunsaturated fatty acid levels in colostrum and child intelligence quotient at age 5–6 years

Bernard JY1, 2, Armand M3, Peyre H4, 5, Garcia C3, Forhan A1, 2, De Agostini M1, 2, Charles M-A1, 2, 6, Heude B1, 2; EDEN Mother-Child Cohort Study Group (Etude des Déterminants pré- et postnataux précoces du développement et de la santé de l’Enfant)

1Epidemiology and Biostatistics Sorbonne Paris Cité Centre (CRESS), Developmental Origins of Health and Disease (ORCHAD) Team, Inserm, Villejuif, France; 2Paris Descartes University, France; 3Centre National de la Recherche Scientifique, Center for Magnetic Resonance in Biology and Medicine, Aix-Marseille Université, Marseille, France; 4Laboratory of Cognitive Sciences and Psycholinguistics (École Normale Supérieure, École des Hautes Études en Sciences Sociales, Centre National de la Recherche Scientifique), École Normale Supérieure, PSL Research University, Paris, France; 5Child and Adolescent Psychiatry Unit, Assistance Publique – Hôpitaux de Paris, Robert Debré Hospital, Paris, France and 6Fondation PremUP, Paris, France

J Pediatr 2017; 183: 43–50

Background: Omega-6 and omega-3 polyunsaturated fatty acid (PUFA), naturally present in human milk, take part in the brain growth during infancy. Available data on the association between PUFA in breast milk and Intelligence Quotient (IQ) of children at 5–6 years of age are discordant.

Methods: A total of 2,002 women were recruited in the study and were tested with their offspring, by using self-administered questionnaires and medical records to obtain general information about feeding habits, alcohol consumption, smoking status, education level, household income. Anthropometric measurements and 5 mL of colostrum were also collected and analyzed. The IQ of 1,080 children at 5–6 years of age was estimated by the use of the Wechsler Preschool and Primary Scale of Intelligence–III.

Results: Breastfeeding was associated with higher IQs than no performed lactation practice, but only in models unadjusted for confounders and demographics, while any breastfeeding duration was associated with both full and verbal IQ. As for associations with PUFAs, low linoleic (LA) and high DHA in colostrum were associated with lower IQs compared with high DHA and low LA and DHA together.

Conclusions: Associations were found between duration of lactation and PUFA levels in colostrum, with children’s IQs at 5–6 years of age.

Comments: This observational study reports the follow-up of a preview survey performed in the French Etude des Déterminants pré- et postnataux précoces du développement et de la santé de l’Enfant mother-child cohort. They found a moderate positive association between lactation duration and colostrum PUFA levels with child’s IQ at age 5–6 years, but, taken the observations together, only a further support to the current recommendations to promote breastfeeding can be derived. Indeed, the observations suggest a positive effect of high DHA and low LA levels in colostrum, respectively, on IQ development. Nevertheless, many factors (either genetic and/or environmental), could be at the origin of the differences in the fatty acid pattern.
Association between maternal intake of n-6 to n-3 fatty acid ratio during pregnancy and infant neurodevelopment at 6 months of age: results of the MOCEH cohort study

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Nutr J 2017;16:23

Background: It is largely agreed that LCPUFAs have an important impact on brain growth during infancy. Furthermore, it is recommended to ensure not only an optimal LCPUFAs intake but also a correct fatty acid ratio of n-6 to n-3 (n-6/n-3 PUFAs) through mothers’ diet.

Methods: This study was conducted by using available data from a community-based prospective birth cohort study: Mothers’ and Children’s Environmental Health. A total of 960 pregnant women were enrolled in the study. The investigators tested them and subsequently their infants at 6 months of age to obtain general and specific information about nutrient intakes, food habits, and consumption by the use of questionnaires and recall methods. They calculated the maternal intakes ratio of n-6/n-3 PUFAs and linoleic acid/α-linolenic acid (LA/ALA).

Furthermore, they assessed infant cognitive and motor development by the Korean Bayley scales of infant development edition II (BSID-II) including the mental developmental index (MDI) and the psychomotor developmental index (PDI).

Results: After adjustment for confounders, negative associations were found between maternal dietary n-6/n-3 PUFA ratios and the MDI and the PDI, and between LA/ALA ratio and the MDI and the PDI in infants at 6 months of age. The risk to observe infants with delayed performance tended to increase with increasing values of the maternal n-6/n-3 PUFA and LA/ALA ratios, respectively.

Conclusions: The authors found a significant negative association of maternal intakes of both n-6/n-3 PUFAs and LA/ALA with infant neurodevelopment and motor function at 6 months of age, but no association between absolute amounts of total n-6, n-3, LA, and ALA and the investigated developmental parameters.

Comments

The investigators suggest to ensure an adequate n-6, n-3, LA and ALA intake in the context of a well-balanced maternal diet during gestation, where balance between fatty acid families could have more impactful than absolute amounts. These recommendations may result in an improvement of global nutritional status of pregnant women that positively influences infant neurodevelopment.
Docosahexaenoic acid and neurodevelopmental outcomes of term infants

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Ann Nutr Metab 2016;69(suppl 1):23–28

**Review:** Seafood, fish oil, and breast milk naturally contain DHA, a fatty acid involved in the normal brain growth. DHA intake of infants occurs predominantly through placental transfer during gestation and through dietary intake after birth. In Western countries, these needs are often not completely covered. Many observational studies and randomized clinical trials focused on DHA supply during pregnancy and/or lactation and cognitive development. Findings do not recommend DHA supplementation of healthy pregnant and lactating women, nor healthy infants because of the presence of controversial and inconclusive evidence about this interaction.

**Comments**
This welcome review, authored by a Cochrane reviewer of PUFA effects, finally underlines once more the “original sin” of research on the role of dietary PUFAs in the first ages of life, from intrauterine life to lactation. Thus, study trials suffer from large degrees of heterogeneity between the studies (dosage, intervention period, outcomes). Future efforts should be able to identify responders to dietary DHA before establishing dose and timing of interventions.

Impact of the n-6:n-3 long-chain PUFA ratio during pregnancy and lactation on offspring neurodevelopment: 5-year follow-up of a randomized controlled trial

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**Background:** LCPUFAs are essential for infant neurodevelopment. Current findings about the role of n-3 LCPUFA supplementation during gestation on children cognition are inconsistent.

**Methods:** In this analysis, 208 healthy pregnant women from Germany were randomized to receive a total dose of 1,020 mg DHA +180 mg EPA +9 mg vitamin E from the 15th week until 4 months postpartum as well as dietary counseling aimed at lowering arachidonic acid intake (intervention group) or to follow a healthy diet during pregnancy according to the German guidelines (control group). Brain growth and function of their children were assessed using a global questionnaire, and a specific hand movement test, and also cord blood LCPUFAs were analyzed. Subsequently, the association with these outcomes was evaluated.
**Results:** Results obtained show neither positive nor negative effects on neurodevelopment of children at preschool age, just inconsistent and not-significant associations, with a change in the n-6:n-3 LCPUFA ratio during gestation.

**Comments** The investigators analyzed data from the INFAT study, and in this article they present secondary results to describe if a reduced n-6:n-3 fatty acid ratio in diet of women during pre and post-natal feeding has positive effects on cognitive function of their children at 4 and 5 years of age. Even if it is widely accepted that LCPUFAs play an important role in brain and neural development, current findings, regarding the impact of n-3 supply during pregnancy on child neurodevelopment, are inconsistent. It is worth noting that the present study has looked at the association between LCPUFAs longer chain derivatives and outcomes, differently than other studies previously mentioned that focused on the ratios between the 2 PUFA precursors. Once more, heterogeneity creates more confusion, that is, at the end, there are no recommendations concerning the present practice, at least in theory.

**Micronutrients**

**Assessing infant cognitive development after prenatal iodine supplementation**

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*Am J Clin Nutr* 2016;104(suppl):928S–934S

**Review:** The investigators first evaluated the prenatal neurodevelopment and the timing of thyroid hormone action on specific brain systems associated with iodine deficiency. Later, they focused their attention on the infant cognitive development and function in prenatal supplementation studies conducted in regions of mild to moderate iodine deficiency.

The authors performed a PubMed search on studies of prenatal iodine supplementation, and they identified the use of these global tests; BSID and Brunet-Lézine scale.

They considered neurodevelopmental outcomes associated with maternal thyroid hormone and maternal iodine status during prenatal period, and tried to evaluate whether specialized cognitive tasks might be more useful than the BSID for assessing the potential effects of prenatal iodine supplementation on cognitive functions.

**Comments** It is largely accepted that an optimal iodine status is crucial for early-life neurodevelopment. There are inconclusive findings on the effects of prenatal iodine supplementation on the cognitive outcomes of children in regions of mild to moderate iodine deficiency. Infant visual attention might be a sensitive measure of infant outcomes because during the prenatal period, the visual attention abilities are sensitive to thyroid hormone. For this reason, the authors propose the use of this measure to improve the reliability of neurodevelopmental and cognitive performance, particularly in regions of mild to moderate iodine deficiency. Multidisciplinary collaborations between scientists would improve research on prenatal iodine supplementation.
Multiple biomarkers of maternal iron predict infant cognitive outcomes

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Dev Neuropsychol 2017;42:146–159

Background: Iron deficiency is common in several countries in the developing world and also in industrialized nations, especially in women.

Methods: The aim of the present observational study was to evaluate the role of the following maternal iron biomarkers: Hemoglobin (Hgb), ferritin, soluble transferrin receptors (sTfR), the ratio of sTfR to ferritin (sTfR:ferritin ratio) and plasma iron, on infant neurocognitive performance. A total of 132 women and their infants were enrolled in the study; mothers completed a demographic form and the Pregnancy Risk Assessment Monitoring System Phase 5 Core Questionnaire at the 3-month visit. Weight and length were measured and infant body mass index (BMI) z-scores were calculated. Venous blood samples were collected and several cognitive tests were performed.

Results: At 9 months, maternal plasma iron correlated positively with novelty preference (memory) and maternal Hgb correlated positively with sustained attention. Furthermore, a negative correlation has been found between plasma iron and neural response variability tertile change.

Conclusions: An improved maternal tissue-level iron may have a role on brain growth and function of children, even in a well-nourished sample. Most studies have been conducted so far in populations with poor iron nutrition, therefore, now other studies in well-nourished countries are needed.

Comments: The authors found inconsistent associations between maternal Hgb and cognitive function. They showed an association with only a single domain, novelty quotient. However, considering multiple iron biomarkers, associations with multiple domains were found. Consequently, we conclude that newer studies with more biologically available pools of iron and specific cognitive domains should be analyzed to enlarge our knowledge on this interesting topic, particularly from well-developed, Western countries.

Impact of maternal selenium status on infant outcome during the first 6 months of life

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Nutrients 2017;9:486

Background: Selenium is relevant for immune and brain development in the first stages of life.

Methods: One hundred fourteen healthy pregnant, 158 healthy, never-pregnant women and their offspring were included in this observational study, performed in Norway. Associations between maternal selenium levels in blood and breast milk on infant brain growth and function during the
First 6 months of life were studied. Clinical data (body weight, nutrition) and the parental questionnaire Ages and Stages were used to evaluate infant neurodevelopment besides selenium analysis of blood and breast milk of mothers.

**Results:** A negative association between maternal selenium level (≤0.90 μmol/L) at 18 weeks of gestation and infant neurodevelopment was found. At 36 weeks of pregnancy, an association between maternal selenium level ≤0.78 μmol/L and an increased risk of infant infection during the first 6 weeks of life has been reported too.

**Conclusions:** Intervention studies are needed to substantiate the hypothesis raised by the observations.

**Comments**
It is widely accepted that selenium is a crucial component for human metabolism. Interest in selenium metabolism has been raised also by the proposed narrow range of recommended dosages for a beneficial effect. Scant experimental data suggest selenium deficiency might negatively affect infant health, in particular immune and brain functions.

Blood selenium levels decreased significantly during pregnancy (p < 0.001), then their levels increased postpartum and remained unchanged from 6 weeks to 6 months. Furthermore, maternal selenium status directly influences the levels of this element in breast milk, as partly expected.

The investigators suggest the opportunity to keep into account a selenium cutoff of 0.90 μmol/L in pregnancy week 18 and 0.78 μmol/L in pregnancy week 36. Intervention studies are needed to obtain specific selenium levels to improve maternal status and infant outcomes.

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**Maternal multiple micronutrient supplementation and other biomedical and socioenvironmental influences on children’s cognition at age 9–12 years in Indonesia: follow-up of the SUMMIT randomised trial**

Prado EL1,2, Sebayang SK1, Apriatni M1, Adawiyah SR1, Hidayati N1, Islamiyah A1, Siddiq S1, Harefa B1, Lum J3, Alcock KJ4, Ullman MT5, Muadz H1,6, Shankar AH1,7

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*Lancet Glob Health 2017;5:e217–e228*

**Background:** Several factors (biomedical and socioenvironmental) play an important role on the brain growth and function.

**Methods:** The authors performed a follow-up of a double-blind, cluster-randomised trial, named Supplementation with Multiple Micronutrients Intervention Trial in Indonesia, in which 262 government midwives were randomly assigned to distribute either iron and folic acid (IFA) or multiple micronutrients (MMN) to pregnant women enrolled in the study.

The IFA capsule contained 30 mg iron as ferrous fumarate and 400 μg folic acid. The MMN capsule contained the same amounts of IFA, plus 800.0 μg retinol, 200.0 IU vitamin D, 10.0 mg vitamin E, 70.0 mg ascorbic acid, 1.4 mg vitamin B1, 1.4 mg vitamin B2 (riboflavin), 18.0 mg niacin,
1.9 mg vitamin B6, 1.6 μg vitamin B12, 15.0 mg zinc, 2.0 mg copper, 65.0 μg selenium, and 150.0 μg iodine. Then 3,068 children were selected for cognitive assessment: nurturing and stimulation from the environment and maternal depression were evaluated using specific tests. Children were tested on cognition and motor performance at local schools and medical information were collected.

**Results:** Participants were divided into 3 groups: a randomly selected representative sample, one from undernourished and one from anemic mothers. In the representative sample and in children of anemic women, tests respectively on procedural memory and on intellectual ability showed positive coefficients of MMN versus IFA. Overall, 18 out of 21 estimates were positive, indicating that the MMN group scored consistently higher than the IFA group.

The regression coefficients for all variables showed that socioenvironmental determinants had stronger associations with school-age cognitive, motor, and socioemotional determinants, as compared with the biomedical factors (22 of 35 coefficients were significant versus 8 of 56). The significant difference in these proportions \( p < 0.0001 \) indicated a more consistent impact of socioenvironmental factors.

**Conclusions:** Results showed higher scores in the MMN group than in the IFA group, indicating a strong impact of maternal MMN supplementation on neurodevelopment and cognitive performance in the offspring, later in life. Furthermore, a preponderant positive role of socioenvironmental determinants on cognitive outcomes of children has been found.

**Comments**

The aim of this study was to examine the effects of a multimineral-multivitamin supplementation, MMN, versus iron plus folate, IFA, only and the impact of biomedical and socioenvironmental factors on child neurocognitive, motor, and socioemotional development.

The authors found a strong link between maternal MMN supplementation and a better cognitive performance of their children compared to IFA, and a stronger impact of socioenvironmental determinants on child neurodevelopment. Therefore, the primary take-home message concerns the necessity of implementing interventions on socioenvironmental determinants, including those to reduce maternal depression and improve educational levels.

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**Microbiome**

**Gut microbiota: a potential regulator of neurodevelopment**

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*Front Cell Neurosci 2017;11:25*

**Review:** More evidence is accumulating that environmental influences during early life may profoundly affect brain development and function later in life. The neurodevelopmental process starts during pregnancy and protracts after birth. The first years of postnatal life represent a time of rapid changes in brain structure and function, where neuronal circuits are particularly sensitive to en-
environmental inputs. It is becoming clear that there is a link between microbiome and neurodevelopment.

After birth, the newborn is colonized with a community of microbes. This postnatal microbial colonization may contribute to developmental programming of epithelial barrier function, gut homeostasis, and angiogenesis, as well as the development and function of the gut immune system. Moreover, this process seems to influence the early-life programming of brain circuits involved in the control of stress response, motor activity, anxiety-like behavior, and cognitive function.

**Comments**

This review considered studies investigating the relationship between brain and gut microbiota. It is clear that several factors play a role on infant gut colonization. Recent evidence has shown comorbidity between neurodevelopmental diseases and the gastrointestinal trait denoting a possible intersection of dysbiosis and neurological illness, that needs to be clarified. The authors considered probiotics, prebiotics, and dietary manipulations as a promising way to improve brain development and function in early childhood.

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**The central nervous system and the gut microbiome**

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**Cell 2016;167:915–932**

**Review:** The influence of microbial community on brain growth has been suggested by several observations. During neurodevelopment, many factors (pre- and post-natally) are involved in this complex process. One of these factors is represented by molecular signal from the gut. In this review, the interaction of the microbiota with central nervous system is widely discussed.

**Comments:** An increasing number of studies hypothesize that perturbations of maternal gut microorganisms may influence fetus development and outcomes during infancy not limited to the immune system and the response to infections, but involving also brain functional domains.

According to other elaborations, antibiotic administration seems related to behavioral disorders, later in life, because of the drastic impact on the microbial community. Accordingly, the present report highlights the interactions of the microbiome-gut-brain axis and underlines the importance of maintaining the healthy commensal gut microbiota to ensure a physiological neurodevelopment. But many details and processes still need to be clarified, and future trials could hopefully investigate this relation as a primary outcome.
**Neurodevelopment: the impact of nutrition and inflammation during early to middle childhood in low-resource settings**

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*Pediatrics* 2017;139(suppl 1):S59–S71

This article will be commented together with the next one.

**Assessment of neurodevelopment, nutrition, and inflammation from fetal life to adolescence in low-resource settings**

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*Pediatrics* 2017;139(suppl 1):S23–S37

**Reviews:** These 2 review articles provide an overview of key definitions, tools, and applications relevant to the assessment of neurodevelopment, nutrition, inflammation, and infection and identify critical research gaps and priorities. The critical periods that have been identified are respectively, from fetal life to adolescence and during early to middle childhood in low-resource settings (LRS).

**Comments**

Children in LRS might be exposed to negative experiences that influence gene expression, which may play a role on the neurodevelopment and also on the behavioral development. For these reasons, children in LRS might be at risk for falling off a normal growth trajectory.

As for the assessment of nutrition, an optimal nutritional status is essential to ensure a normal neurodevelopment. Malnutrition, considered as undernutrition, deficiencies in micronutrients, and overweight/obesity, has been identified as risk factors to the developing brain.
Another aspect considered in these reports is the role of inflammation on brain growth and function. The available evidence suggests that fetal exposure to maternal infection and inflammation may have a profound effect on neurodevelopment during childhood.

The interactions between inflammation and nutrition are complex and bidirectional. Microbiome and environmental conditions represent 2 recent areas of interest that may have an interactive effect in later life.

Newer and original studies are needed to clarify the direct effects of inflammation and nutrition on neurodevelopment and, in particular, interventions that can favorably impact these relationships.

**Association between maternal nutritional status in pregnancy and offspring cognitive function during childhood and adolescence: a systematic review**

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*BMC Pregnancy Childbirth 2016;16:220*

**Background:** During gestation, food habits and consequently nutritional status of women are crucial for the normal brain growth of their children.

**Methods:** The authors have focused their attention on BMI, height and weight; status or intake of selected single micronutrients (vitamins D, B1, B6, B12 and folate, and iron), and dietary intake of macronutrients (carbohydrate, protein, and fat) in pregnant women. From the database search, any measure of neurocognitive outcomes in children up to 18 years of age, were examined. They observed clinical trials, observational studies from retrieved literature and identified 16,143 articles published in English from January 1960 to October 2014, excluding case reports and animal studies.

**Results:** Based on inclusion criteria, 38 articles were selected. The investigators obtained controversial results. Maternal obesity and vitamin D deficiency seem to be associated with lower neurocognitive performance of their children. Most studies found no association between maternal vitamin B12 and iron status and offspring cognitive function.

Two trials, one of maternal carbohydrate/protein supplementation and the other of folic acid supplementation showed no effects on the children’s neurocognitive outcomes. Since positive findings were mainly in observational studies, residual confounding limits conclusions.

**Conclusions:** There is inconclusive evidence to confirm or refute the association of maternal nutritional status (BMI, single micronutrient or macronutrient intakes) with offspring cognitive function.

**Comments**

The major limitation in the present knowledge on this topic is represented by the very limited number of studies and/or observations from the poorer developing countries. Indeed, mothers coming from these settings should reasonably be more exposed to nutritional deficiencies, and yet more advantaged by specific supplementations. It is likely the only way to convincingly show the potential of a given nutrient on brain functional development.
Maternal dietary patterns during pregnancy and intelligence quotients in the offspring at 8 years of age: findings from the ALSPAC cohort

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Matern Child Nutr 2018;14:e12431

Background: Maternal nutritional status during gestation has been identified as an important aspect of the developing brain of offspring. Children of women who have an adequate dietary intake during pregnancy show better cognitive outcomes compared to children of women who follow an unbalanced diet.

Methods: The aim of the present study was to examine the links between maternal dietary patterns during pregnancy and IQ of their children at 8 years of age, assessed using the Wechsler Intelligence Scale for Children.

Results: Maternal food habits were obtained by cluster analysis during pregnancy; 47 food items were used and accordingly mothers classified into 3 best described clusters: “fruit and vegetables,” “meat and potatoes,” and “white bread and coffee.” Pregnant women who were classified in the fruit and vegetables cluster had offspring with higher average IQ compared to the other 2 groups.

Conclusions: Maternal diet in pregnancy may promote an optimal neurodevelopment in offspring when following a diet rich in fruit and vegetables.

Comments: In previous publications, the authors concluded that current evidence about the role of BMI, single micronutrient or macronutrient intakes of pregnant women on offspring cognitive function is inconclusive.

In the second study, the results showed that children of women in “fruit and vegetables” cluster had the highest mean verbal, performance, and full-scale IQ scores at 8 years of age compared to children with mothers classified in the others clusters, and children of women in “white bread and coffee” had the lowest average scores. This study, whose observations are highly interesting like other previously published from the same group, presents some limitations, as well as, loss to follow-up of subjects from the original sample, missing data, and underestimation or overestimation of dietary intake through the food frequency questionnaire.

Therefore, many unclear aspects may still confound the evidence. The general common-sense recommendation is still working, that is, during gestation, maternal food habits should be optimal to ensure a normal neurodevelopment in the offspring. Newer and original studies are needed, in particular in less well-nourished populations, to examine these associations.
From neuro-pigments to neural efficiency: the relationship between retinal carotenoids and behavioral and neuroelectric indices of cognitive control in childhood

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Int J Psychophysiol 2017;118:1–8

Background: Lutein and zeaxanthin are 2 carotenoids present in nature and in the human diet, highly concentrated as macular pigments in the foveal retina of primates. Lutein, in particular, is known to accumulate across all cortices and brain membranes. Recent studies have focused the attention on the possible function of lutein on maintaining the cognitive abilities in older adults.

Few investigations have examined the relationship between lutein and cognition in living children. The present study is the first to explore lutein in relation to any brain-based measure of cognition in preadolescent children.

Methods: By 2 testing sessions, authors examined participants’ cognitive performance (response accuracy and reaction time). Children completed Macular Pigment Optical Density assessment, a retinal measure that is sensitive to cognitive measures, and an educational achievement test. Furthermore, an electroencephalogram was recorded.

Results: Results presented suggest that lutein is involved in cognitive control. Children with higher Macular Pigment Optical Density values show better neural efficiency but with neural markers of lower cognitive load.

Conclusions: The potential positive function of lutein to cognitive performance should be investigated during the lifespan to extend present findings and improve cognition in childhood.

Comments Welcome to the entry into the arena of food for thought, another micronutrient, lutein, is still under discussion to extract a functional role on brain in early life. Whatever the results and the role, we expect harmonization of studies before reaching non-conclusive evidence for other most popular compounds.

Overall Summary

The indications that can be drawn from the presented papers may be summarized in few points:

1 When studying a nutrient, harmonization among studies (and not just in the field of effects on cognition) is mandatory, not to waste money with heterogeneous study designs and allowing for comparisons between results, in order to reach firm conclusions.

2 Newer and most solid neurodevelopmental tests are needed, considering different ages and cultural background, and not contaminated by the use in clinical practice of scales born to score the mental handicap, since we need to study effects within the normal range of intellectual achievement.

3 While most controversial studies probably arise from the typical western models, where all conditions are more favorable in general, and differences of effects are blunted, future studies should
consider trials in developing and transition countries, where effects on developmental achievement could have more striking effects.

If studies and research in the field do not evolve further, it is hard that in the next years we could evolve from the present status, where many single studies suggest mild effects of intervention (if any) and systematic reviews and metanalyses end with the frustrating sentence on “more well-designed studies are needed.”