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CurrentViews©

IN PEDIATRIC NUTRITION

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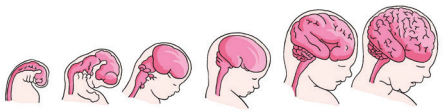
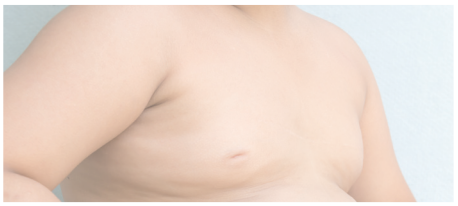
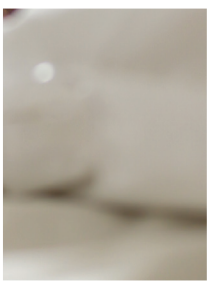
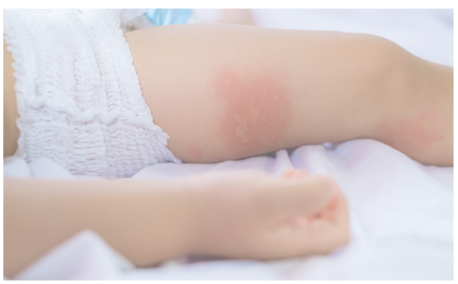
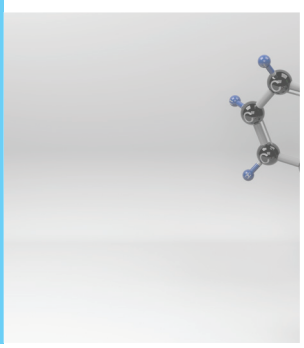
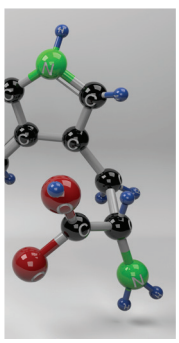
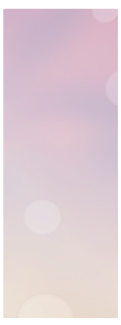
Metabolic Disorders



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EDITOR'S NOTE

The world of Medicine has made great advances since its early days. In recent years we have had the privilege of witnessing developments in understanding the pathogenesis of many of the diseases burdening humankind. It is frustrating, though, to realize that most of this up-to-date knowledge does not reach its natural recipients, who are specialist in each specialty working in daily practice. Thus, we believe that the need for an informative journal is obvious and self-explanatory.

For this reason, CCM fills the gap in continuing medical education to benefit every day clinical practice, by publishing this innovative series of Current Views. In every issue, readers will find a review article and several summary articles. *Current Views in Pediatric Nutrition* was designed to solve the problem of information overload for specialist physicians. Each journal is compiled by the CCM editorial team based on an ongoing review of the international literature, and articles are selected for review and citation on the basis of their relevance to clinical practice.

Current Views in Pediatric Nutrition provides specialists with an attractive means of continuing medical education that demonstrates the best of critical thinking and is a source of, and a catalyst for, new ideas and learning. The editors and medical advisors at CCM have made every effort to search the international literature to present the most current, interesting and cutting edge articles, in order to make *Current Views in Pediatric Nutrition* a respected and useful tool of physicians with one aim: to provide a good service to their patients. For this issue, we have retrieved information from several well respected peer reviewed journals:

Am J Clin Nutr.
Ann Nutr Metab
Br J Nutr.
Foods.
Front Neuroendocrinol
Front Pediatr.
Gut Microbes.
J Allergy Clin Immunol Pract.
J Pediatr (Rio J)
J Pediatr Gastroenterol Nutr.
J Pediatr.
Neonatology.
Neuroimage.
Nutrients.
Nutrition.
Pediatrics.
PLoS One.
Prev Med.
Trends Microbiol.

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Editorial Board Members

A Note from the Regional Editors

Progress in Pediatric Nutrition has continued at a spectacular pace culminating in a rapid surge in the number of increasingly precise articles on information about the assessment of growth, the nutritional status assessment and feeding guidelines, biochemical evaluation of nutritional status, infant nutrition, enteral nutrition, parenteral nutrition, nutritional management in health as well as in disease for pediatric residents powered by research. The cumulative knowledge of the complexities of Pediatric Nutrition continues to be the foundation of new advances across the clinical care continuum.

Discoveries in the fields of metabolism, genomics and immunology have been particularly fruitful and have firmly established two new pillars of clinical care. These exciting fields of research also show immense promise for the future. Furthermore Clinical Medical Societies have been updating their Guidelines of Pediatric Nutrition.

Current Views in Pediatric Nutrition was designed to solve the problem of information overload for specialist physicians. Each journal is compiled by the Regional Editors based on an ongoing review of the international literature, and articles are selected and then summarized for citation and review on the basis of their relevance to clinical practice.

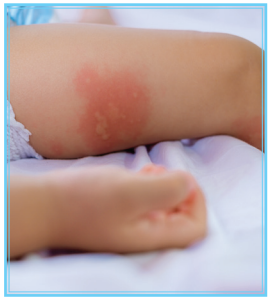
Current Views in Pediatric Nutrition mainly caters to the needs of the professionals, researchers, clinical practitioners and medical practitioners in the field of Pediatrics. Our content covers topics that advance clinical practice, and tackle issues related to global Pediatrics. The Regional Editorial Board's aim is to include the most complete and reliable sources of information and discoveries ongoing in Pediatrics and Nutrition research and treatment. The Regional Editors work as a distinguished team of experts to ensure the highest standards of selection. All relevant articles in the international literature are carefully considered and once selected all materials are promptly processed and published.

The stringency of selecting and voting on state of the art articles was done by our respected Regional Editorial team members who are listed within the journal. Our fundamental purpose is to advance clinically-relevant knowledge of Pediatric Nutrition, and improve the outcome of prevention, diagnosis and treatment of pediatric disease.

In this third issue, due to the spectacular developments seen lately, original research articles, early reports and review articles covering key points, potential pitfalls, and management algorithms which allow for rapid-reference, and link with the latest evidence, guidelines and protocols from ESPGHAN and NASPGHAN covering the major professional society recommendations for clinical practice have been included.

We believe that the readers will find many topics of interest related to their everyday practice.

The Regional Editorial Board



Feature Article

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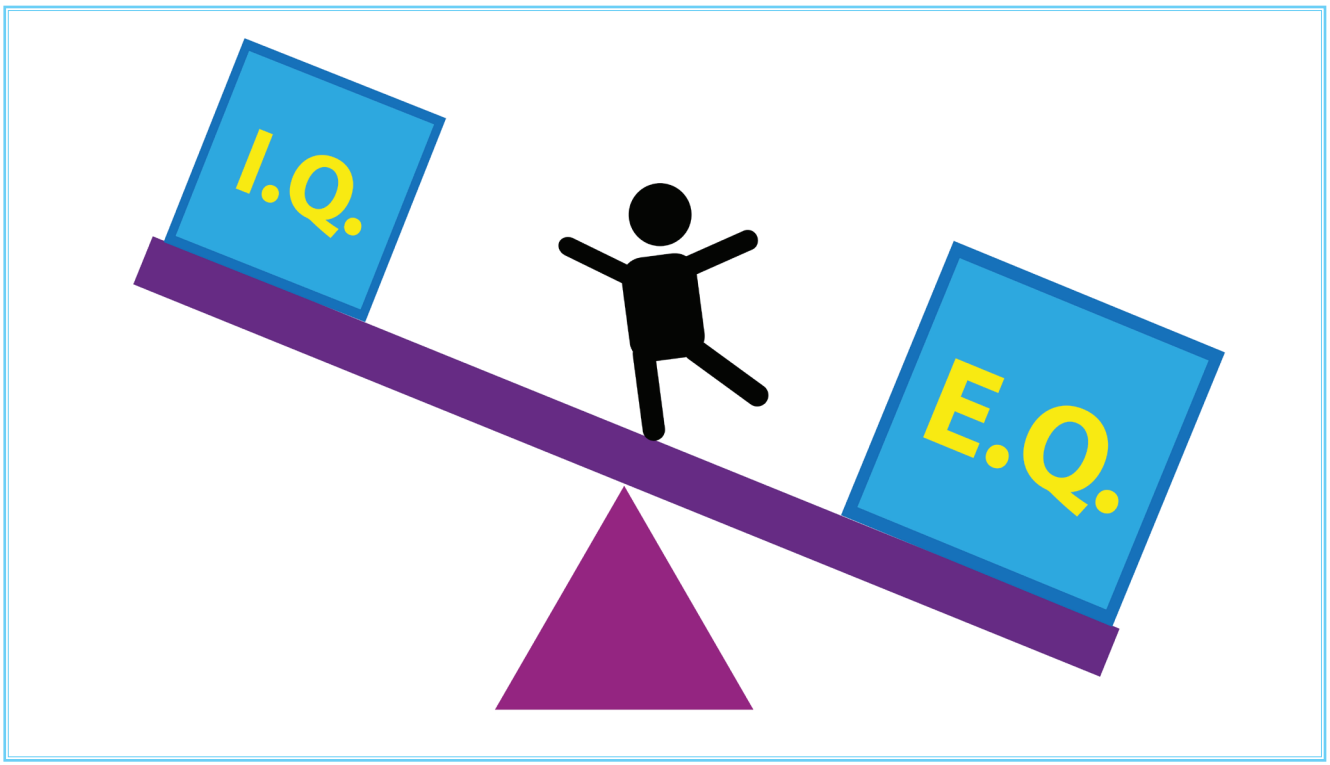
Gastrointestinal Disorders

Metabolic Disorders

The Effect of Diet on the Mental Performance of Children



Introduction

In humans, the critical window of brain development is between the third trimester of gestation and 2 years of age.[1] Intra-uterine and neonatal insults have long-term detrimental effects on neurodevelopmental outcomes, which are not regulated only genetically.[2] It is known that nutrients regulate brain development during gestation and early postnatal life. Therefore, early nutrition during these critical windows of rapid brain development might be essential for later cognitive functioning and behaviour.[1]

The newborn human brain undergoes a remarkable transformation in form and function beginning at the age of extra-uterine viability at approximately 23-24 weeks post-conceptional age (PCA) through the first two years of life.[3,4]

Early Brain Development and Nutritional Status

The growth rate of the brain during prenatal/postnatal period is among the highest during life span. The neonatal brain in the human consumes 60% of the body's total oxygen and therefore caloric consumption.[3] The positive or negative effects of nutrients on the brain are based on the timing, dose and duration of the exposure. This principle resides biologically in the fact that the brain is not a homogenous organ, but rather, it is made up of distinct regions (eg, hippocampus, cortex, striatum, cerebellum) and processes (eg, myelination, neurotransmitters), each of which has a different developmental trajectory and set of nutrient requirements.[3]

Some nutrients appear to have a stronger effect on brain development during gestation and early infancy,

such as protein, Fe, Zn, Se, folates, long-chain PUFA and vitamin D, among others.[1,5,6] Sufficient protein and iron and resultant brain outcomes is perhaps most expansive, but work supporting a role for other macronutrients, including polyunsaturated fatty acids (PUFAs), and micronutrients, including zinc, iodine, and vitamin B_{12} and brain development is substantial and growing.[3]

Macronutrient Effects on Brain Development

***Protein*:** Macronutrient status and its anthropometric correlate, growth velocity, follow the timing, dose, and duration rules as they relate to brain development. Improved linear growth is an important finding because linear growth prenatally and in early infancy is a consistent predictor of neurobehavioral outcomes.[3]

Improving protein intake and linear growth in early life is critical to later cognition.[3] Pongcharoen et al. related the Intelligence Quotient (IQ), as measured by the Wechsler Intelligence Scale, of 560 nine-year-old Thai children to indices of birth size and rate of postnatal growth. Researchers found that infant length at birth and throughout the first 12 months of life were strongly positively correlated with child IQ at 9 years of age. Early infancy (birth to 4 months) weight was also associated with IQ at 9 years. No index of growth after 12 months was related to IQ in later childhood.[7]

***Long-chain polyunsaturated fatty acids (LCPUFAs)*:** The effects of early-life supplementation of LCPUFAs on child development has been extensively studied. Although recent meta-analyses of LCPUFAs during gestation, infancy, and early childhood report no significant benefit with regard to cognition and attention, several smaller studies suggest that benefit is apparent on more specialized tasks assessed in older children rather than in infants and toddlers.[3,8,9]

The most abundant LCPUFAs in the brain and those critical for proper development and function of the brain, nervous system, and eye are *n*-3 docosahexaenoic acid (DHA; 22:6*n*-3) and *n*-6 arachidonic acid (AA; 20:4*n*-6).[10,11] DHA and AA are either obtained directly from the diet or synthesized in the body from the essential fatty acids (FAs), linoleic acid (LA; 18:2*n*-6) and α-linolenic acid (ALA; 18:3*n*-3), through a multi-step process that is slow and inefficient in humans.[10,12]

Infants and young children have high nutritional demands in order to support adequate growth and development, particularly during the transition from complementary feeding at 12 months of age to a mixed and varied diet at 36 months of age.[10,13] Only certain foods contain LCPUFAs at concentrations sufficient for these needs. Although dietary recommendations for LCPUFAs and essential FAs in late infancy and early childhood (6-24 months) are specifically emphasized for this age range, they vary widely across the world.[10] Optimal intake levels are not conclusively established and there are little data to estimate daily intake of preformed LCPUFAs in late infancy and early childhood.[10,12]

A recent study found no benefit of LCPUFA-fortified formula in infants at 18 months on standardized developmental tests, but reported benefit in children at 4-6 years of age on more specific tasks, such as rule-learning, inhibition, and vocabulary tests.[10,14]

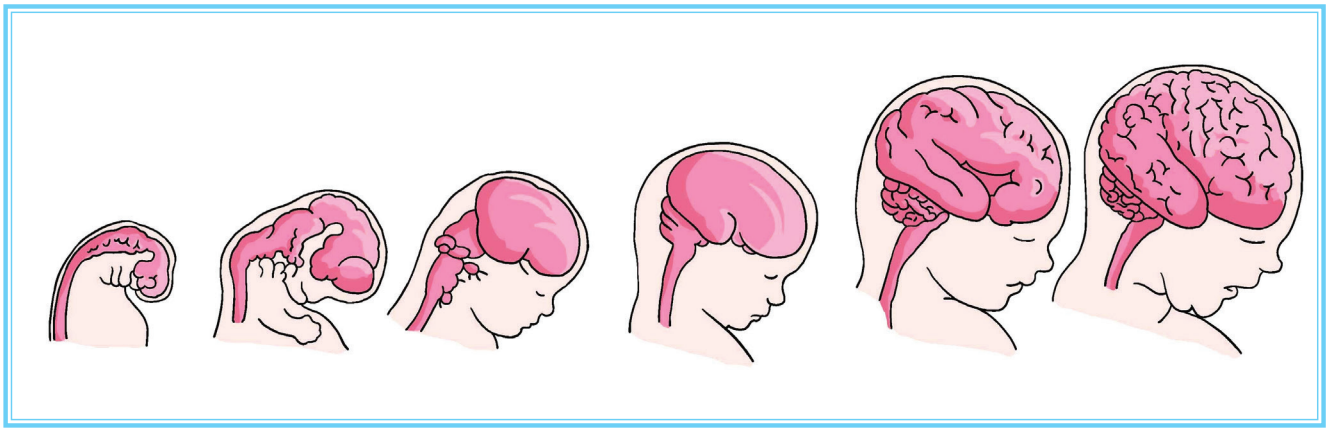
Micronutrient Effects on Brain Development

The clinical literature with regard to early life provision of micronutrients, including iron, iodine, zinc, and vitamin B_{12}, and brain development is also growing.[3]

Iron: Iron deficiency anemia is a global public health problem considered to be the "most common and widespread nutritional disorder in the world."[15,16] Iron deficiency anemia in infancy is associated with negative health outcomes, including poorer cognitive, motor, and socioemotional development.[17] In many countries, it is routine to supplement infant formula and foods with iron to prevent iron deficiency anemia.[15]

The risk of iron deficiency is greatest in pregnancy and early infancy and childhood, coinciding with periods of peak need for iron for the developing fetal and infant brain. The importance of the timing of iron supplementation and maintenance of early life iron sufficiency on distinct neurobehavioral outcomes is clearly demonstrated.[3]

Despite routine iron fortification of infant formulas, there is limited research assessing the optimal level of iron fortification and long-term effects on the developing brain.[18] Expert organizations worldwide differ on the recommended level. The American Academy of Pediatrics Committee on Nutrition recommends that formula-fed infants receive formula containing 179-214 mmol/L (10-12 mg/L) of iron



beginning at birth.[19] The European Society of Pediatric Gastroenterology, Hepatology and Nutrition recommends lower concentrations of iron in infant formula (32.2-140.0 mmol/L; 4-7 mg/L),[20] with some countries recommending follow-on formulas with higher concentrations of iron after 6 months of age.[15]

Previous studies reported lower developmental test scores in 10-year-old children randomized to iron-fortified formula (12 mg/L) in infancy compared with those randomized to low-iron formula (2.3 mg/L). Effects varied by 6-month hemoglobin concentration. Specifically, children with higher 6-month hemoglobin concentrations (>128 g/L) randomized to iron-fortified formula had lower scores compared with those randomized to low-iron formula.[15] Children with lower 6-month hemoglobin concentrations (<10^5 g/L) who received iron-fortified formula had better performance compared with those supplemented with low-iron formula.[15] In a 10-year assessment, Lozoff et al found that participants who received any level of iron supplementation performed better on neurocognitive and socioemotional measures than those who did not receive supplementation.[21]

Studies demonstrating long-lasting consequences of untreated iron deficiency in infancy, i.e., before 12 months of age, reinforce the supplementation studies showing benefit of early introduction of iron. Such consequences include poorer inhibitory control (diminished attentional control and greater risk taking) at 10 years of age and persistent alternations in brain functional connectivity in adults who were iron-deficient as infants.[3,22]

***Iodine*:** Iodine deficiency is the leading cause of preventable impaired mental function worldwide, affecting an estimated two billion people. The developing brain is most susceptible to iodine deficiency during the first trimester, when fetal T_3 production depends entirely upon supply of maternal T_4. The harmful impact of severe iodine deficiency (populations in which 30% of school-aged children have goiter and median population urinary iodine concentration is below 20) on brain development is established.[3]

Zinc: Meta-analyses have failed to find a significant effect of early zinc supplementation on child cognitive and motor outcomes, although disparate study designs and effect sizes in the combined datasets were noted.[23] Nevertheless, fetuses of zinc-deficient mothers demonstrate decreased movement, lower heart rate variability, and altered autonomic nervous system stability. They additionally demonstrate decreased preferential looking behavior, but do not display differences in global cognitive tests.[3]

***Vitamin B_{12}*:** Sufficient vitamin B_{12} is required for neuronal development and myelination. In a review of 48 case reports of infant vitamin B_{12} deficiency, Dror and Allen, report that all cases resulted from maternal deficiency, and two-thirds of the 48 reports reported developmental regression in infants with B_{12} deficiency, marked by nerve demyelination and cerebral atrophy.[24] A recent study of maternal B_{12} supplementation reported no difference in global cognitive scores at 9 months in infants of supplemented mothers.[25]

Folate: Previous studies have suggested that prenatal maternal folate deficiency is associated with reduced prenatal brain growth and psychological problems in offspring.[26] Children with prenatal homocysteine levels >9·1 μmol/l had

a significantly lower (7 points) IQ at age 6 years. Although the effect estimates were in the same direction, no significant associations between prenatal folate levels or vitamin B_{12} levels and child intelligence were found.

Prenatal folate levels predicted performance on the language, memory/learning and the visuo-spatial subdomains of the NEPSY-II. There was only a trend in the association between prenatal folate levels and NEPSY-II total score. Prenatal homocysteine levels predicted performance on the language and visuo-spatial subdomains of the NEPSY-II. No associations between prenatal plasma vitamin B_{12} and NEPSY-II performance were found. The correlation between the SON-R and the NEPSY-II was r 0·181; p= 0·005.[26]

Health Benefit of Human Milk Oligosaccharides

Breast milk is the natural and ideal food for infants, providing the energy and nutrients that every infant needs during the first four to six months of life in the correct quality and amount. Infants who are breastfed for shorter periods or are not breastfed suffer more infectious diseases, such as gastroenteritis and acute otitis media, more immune-mediated diseases, have a lower intelligent quotient (IQ) and are likely to have a higher risk of being overweight and type 2 diabetes in later life.[27] The composition of breast milk is unique. Aside from nutrients for the infant's healthy growth and development, it contains thousands of bioactive substances,[28] including human milk oligosaccharides (HMOs).[29] HMOs are non-digestible carbohydrates. Although they have little nutritional value for the infant, HMOs are the third largest solid component in human milk after lactose and lipids.[30] Compared to human milk, oligosaccharide concentrations in the milk of farm animals, such as cows, goats, and sheep are 100–1000-fold lower.[27]
HMOs and their metabolic products, such as sialic acid, have a role in brain development, neuronal transmission, and synaptogenesis. HMOs are a source of sialic acid, which is an essential nutrient for optimal brain development and cognition.[31,32] L-fucose and 2′-fucosyllactose (2′- FL) stimulate brain development. The HMOs 3′-sialyllactose and 6′-sialyllactose support normal microbial communities and behavioral responses during stress by modulating the gut-brain axis.[33]

Sphingomyelin

Sphingomyelin (SM) supports brain myelination, a process closely associated with cognitive maturation. The presence of SM in breast milk suggests a role in infant nutrition; however, little is known about SM contribution to healthy cognitive development.[34] SM levels were quantified in infant nutrition products fed in the first three months of life and associated with myelin content (brain MRI) as well as cognitive development (Mullen scales of early learning; MSEL). Higher levels of SM were significantly associated with higher rates of change in verbal development in the first two years of life, as well as, higher levels of myelin content at 12–24 months, delayed onset and/or more prolonged rates of myelination in different brain areas. These findings indicate an impact of dietary SM on cognitive development in healthy children, potentially modulated by oligodendrocytes and increased axon myelination. Future research should include randomized controlled trials to substantiate efficacy of SM for cognitive benefits together with preclinical studies examining SM bioavailability and brain uptake.[34]

Nutrition, Brain and Neurodevelopment in Preterm Infants

Infants born at <30 weeks of gestation are at high risk of postnatal growth failure because of medical morbidities that increase energy requirements and because the immature gastrointestinal tract impedes delivery of enteral nutrition.[35] The provision of adequate ex utero nutrition in preterm infants is challenging. Consequently, postnatal growth failure is common and associated with poorer neurodevelopmental outcomes.

Currently, "adequate" nutrition for the preterm infant is designed to "provide nutrients to approximate the rate of growth and composition of weight gain for a normal fetus of the same post-menstrual age and to maintain normal concentrations of blood and tissue nutrients".[36]

The preferred source of nutrition for preterm infants is human milk from the infant's own mother. However, it has been long known that very/extremely preterm infants fed exclusively breast milk cannot match intrauterine growth patterns and may end up with extra uterine growth restriction. Therefore, human milk is fortified with a Human Milk Fortifier (HMF) to enhance protein, caloric, vitamin and mineral intake. It is important to note that extremely

preterm infants are fed fortified human milk, regardless of the actual content of the human milk itself. From a Cochrane systematic review on the use of HMF for preterm nutrition it was concluded that HMF slightly increased in-hospital growth rates, but there was not enough evidence to suggest that feeding preterm infants with a standard amount of multi-nutrient fortified breastmilk improves important developmental outcomes.[36]

A systematic review published in 2016 reported that long chain polyunsaturated fatty acid supplementation of formula or breast milk during the "lactation" period in preterm infants was associated with significant improvement in neurodevelopment at toddler age.[37] However, no studies to date have shown that increased total fat intake over the same time period confers the same benefit.[36]

Optimal early nutrition providing adequate amounts of all macronutrients and micronutrients is essential for normal brain development, and enhanced nutrition in the first weeks after birth has the potential to improve neurodevelopmental outcomes. To date, there is insufficient evidence to determine the effect of higher early intravenous amino acid intake on neurodevelopment. However, few nutrition trials in extremely preterm babies have been designed to test the effect on neurodevelopment, and those that have been performed are heterogeneous in design and reporting of results. Numerous other questions relating to nutrition and its impact on neurodevelopment remain to be answered, including the optimal intravenous nutrition solutions and electrolyte intakes, the optimal energy: protein ratio, and whether girls and boys require different nutritional intakes. Techniques such as advanced MRI provide more timely, objective and specific assessments than traditional developmental screening tools and may provide useful early markers to assess nutritional interventions whilst waiting for longer-term follow-up to be completed. Future research will be of greatest value if trial designs result in separation of nutritional intakes between groups, ensure adequate energy, macronutrients and micronutrients, and are powered to assess a primary outcome of neurodevelopment separately in girls and boys. The development of minimal reporting sets and core outcome sets for nutrition research will aid future meta-analysis.[38]

Evidence of Nutritional Effects on the Brain from Brain Imaging

The use of brain imaging techniques to examine brain structure and function has great potential to give timely, accurate and objective information about the relationships between nutritional interventions, growth and neurodevelopment. Decreased brain volume at term-equivalent age is related to both white matter abnormalities and decreased deep nuclear grey matter volume.[39] Preterm babies have high rates of white matter abnormalities which are visible on conventional MRI in the form of loss of volume with enlarged ventricles, delayed cortical maturation and diffusion abnormalities. Diffusion-tensor MRI uses the diffusion of extracellular water molecules to infer the brain's microstructure. Altered regional diffusion measures in very preterm infants imaged at term-equivalent age have been associated with impaired motor and cognitive development at age seven. Fractional anisotropy (FA) is a measure used in diffusion imaging which reflects fibre density, axonal

diameter and myelination in white matter. In the cerebral cortex, the radial organization that is expected early in the third trimester is reflected in high FA that decreases to term-equivalent age.[39]

The Effect of Diet on the Physical and Mental Development of Children – Views of Parents and Teachers

Although the impact of diet on physical health is an important public health issue, less attention has been devoted to the relationship between nutrition and children's mental development. The views of parents and teachers about the extent to which diet affects physical and mental development of children were compared in four European countries.[40]

An online questionnaire (developed in English and translated) was circulated through a market research agency. Participants were parents or teachers of children aged 4–10 years without learning or behavioral issues. Questionnaires were returned by 1606 parents (401 in England, Germany and Hungary; 403 in Spain) and 403 teachers (100 in each country, except for 103 in Hungary). Teachers were older than parents (35·3% vs. 18·3 % over 45 years; $p<0·001$) and less likely to smoke (15·9% vs. 26·3%, $p<0·001$). There was no difference between the proportions of parents and teachers who felt that a child's physical development depended very much/extremely (vs. moderately/slightly/not at all) on diet (overall 79·8 %). Lower proportions of both groups thought that mental development was very much/extremely influenced by diet (67·4 %). In the regression modelling, believing that physical and mental performance was greatly influenced by diet was significantly and positively associated with living in Hungary, scoring higher on a measure of General Health Interest and (parents only) level of education attained. Differences existed among countries in most views. Lower levels of awareness of the importance of diet for brain development and cognition (compared with physical health outcomes) indicate the potential for educating consumers, especially parents with lower educational attainment.[40]

Cognitive processes are complex and experimental designs are confounded by a range of factors (such as the time of day the measurement is made or composition of the foods used in interventions). Socio-economic factors (such as parenting, access to education and resources at home) influence background cognitive competence. Moreover, mood, motivation and arousal (themselves affected by nutrition) can additionally influence mental performance in various ways. [40]

The effect of Nutrient Intake in Children Behavior

Unadjusted analyses comparing children who had been breastfed for at least 3 months showed similar behavior and performance in all the domains compared with the higher protein and lower protein children.[1]

Adjusted analyses, considering factors that could influence neurodevelopment, such as parental education level and nationality, mother's age and marital status, maternal smoking, child's gestational age at birth, delivery type and head circumference at birth and at 8 years of age. These adjusted analyses confirmed no differences in any of the neuropsychological domains and behavior between 8-year-old children fed the higher or the lower protein formula during the 1st year of life.[1]

Conclusion

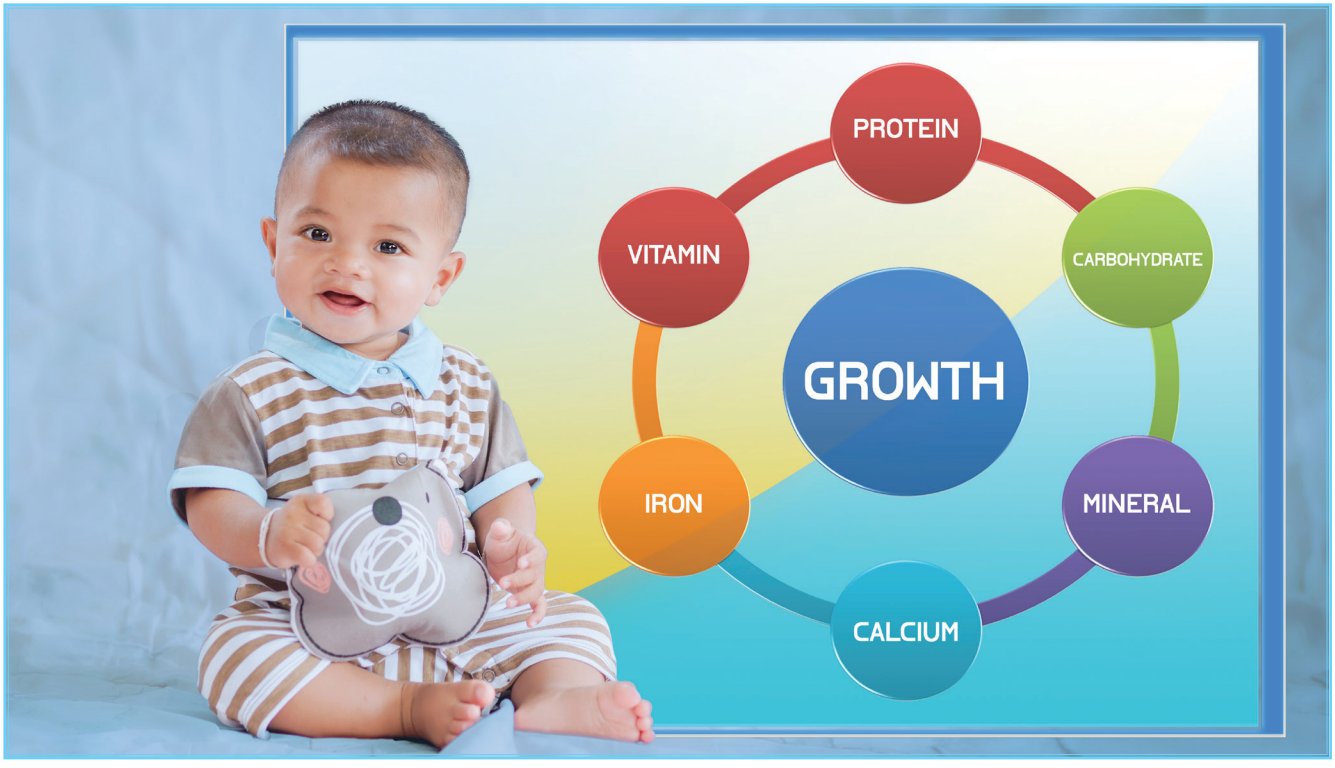
Whereas all nutrients are needed for the development and function of the brain, certain nutrients have high impact on early brain development, including protein fats, iron, zinc, iodine, and vitamin B_{12}. The impact is greater in the fetal and early postnatal period because of the high metabolic demands of the brain at that age. The positive or negative neurobehavioral effects of these nutrients depends on the timing, dose, and duration of provision or deprivation. Timing appears to play an important role because of the non-homogenous nature of regional brain development and because of the unequal distribution of prevalence of nutrient deficits in a population.

Ensuring adequate fetal loading of nutrients through better maternal care during pregnancy via provision of adequate nutrition and reduction of obesity, hypertension, and glucose intolerance appears to be key to fostering postnatal nutrient sufficiency. For the term neonate, human milk provides the optimal support for neurodevelopment, whereas for at risk populations such as preterm infants, early identification and correction of nutrient deficits is essential to maintain the brain on trajectory through critical periods of development.[3]

References

1. Escribano J et al. Mental performance in 8-year-old children fed reduced protein content formula during the 1st year of life: safety analysis of a randomised clinical trial. *Br J Nutr*. 2019 Sep;122(s1):S22-S30. doi: 10.1017/S0007114515000768.
2. Laus MF, Vales LD, Costa TM, et al. Early postnatal protein-calorie malnutrition and cognition: a review of human and animal studies. *Int J Environ Res Public Health* 2011;8, 590–612.
3. Acta Georgieff MK, Ramel SE, Cusick SE. Nutritional influences on brain development. *Paediatr*. 2018 Aug;107(8):1310-1321. doi: 10.1111/apa.14287.
4. Lagercrantz H. Origins of the Mind and Basic Construction of the Brain. In: Lagercrantz H, editor Infant Brain Development Springer; 2016 114
5. De Souza AS, Fernandes FS and do CM. Effects of maternal malnutrition and postnatal nutritional rehabilitation on brain fatty acids, learning, and memory. *Nutr Rev* 2011; 69, 132–144.
6. Currenti SA. Understanding and determining the etiology of autism. *Cell Mol Neurobiol* 2010; 30, 161–171.
7. Pongcharoen T, Ramakrishnan U, DiGirolamo AM, Winichagoon P, Flores R, Singkhornard J, et al. Influence of prenatal and postnatal growth on intellectual functioning in school-aged children. *Arch Pediatr Adolesc Med*. 2012; 166:411–6.
8. Jasani B, Simmer K, Patole SK, Rao SC. Long chain polyunsaturated fatty acid supplementation in infants born at term. *Cochrane Database of Systematic Reviews*. 2017; (3) Art. No.: CD000376. doi: 10.1002/14651858.CD000376.pub4
9. Delgado-Noguera MF, Calvache JA, Bonfill Cosp X. Supplementation with long chain polyunsaturated fatty acids (LCPUFA) to breastfeeding mothers for improving child growth and development. *Cochrane Database Syst Rev*. 2010; 12:CD007901.
10. Kim Y, Kim H, Kwon O. Dietary intake of *n*-3 and *n*-6 polyunsaturated fatty acids in Korean toddlers 12-24 months of age with comparison to the dietary recommendations. *Nutr Res Pract*. 2019 Aug; 13(4):344-351. doi: 10.4162/nrp.2019.13.4.344.
11. Bazinet RP, Layé S. Polyunsaturated fatty acids and their metabolites in brain function and disease. *Nat Rev Neurosci* 2014;15:771-85.
12. Keim SA, Branum AM. Dietary intake of polyunsaturated fatty acids and fish among US children 12-60 months of age. *Matern Child N*utr 2015;11:987-98.
13. Gibson S, Sidnell A. Nutrient adequacy and imbalance among young children aged 1-3 years in the UK. *Nutr Bull* 2014;39:172-80.
14. Colombo J, Carlson SE, Cheatham CL, Shaddy DJ, Kerling EH, Thodosoff JM, et al. Long-term effects of LCPUFA supplementation on childhood cognitive outcomes. *Am J Clin Nutr*. 2013; 98:403–12.
15. Gahagan S et al. Randomized Controlled Trial of Iron-Fortified versus Low-Iron Infant Formula: Developmental Outcomes at 16 Years. J Pediatr. 2019 Sep;212:124-130.e1. doi: 10.1016/j.jpeds.2019.05.030.
16. World Health Organization (WHO). Daily iron supplementation in infants and children. Geneva, Switzerland: World Health Organization; 2016.
17. Georgieff MK. Long-term brain and behavioral consequences of early iron deficiency. *Nutr Rev* 2011;69(Suppl):S43-8.
18. Hare DJ, Arora M, Jenkins NL, Finkelstein DI, Doble PA, Bush AI. Is early-life iron exposure critical in neurodegeneration? *Nat Rev Neurol* 2015;11:536-44.
19. Baker RD, Greer FR. Committee on Nutrition American Academy of Pediatrics. Diagnosis and prevention of iron deficiency and iron deficiency anemia in infants and young children (0-3 years of age). *Pediatrics* 2010;126:1040-50.
20. Domellöf M, Braegger C, Campoy C, Colomb V, Decsi T, Fewtrell M, et al. Iron requirements of infants and toddlers. *J Pediatr Gastroenterol Nutr* 2014;58:119-29.
21. Lozoff B, Castillo M, Clark KM, Smith JB. Iron-fortified vs low-iron infant formula: developmental outcome at 10 years. *Arch Pediatr Adolesc Med* 2012;166:208-15.
22. Algarin C, Karunakaran KD, Reyes S, Morales C, Lozoff B, Peirano P, et al. Differences on brain connectivity in adulthood are present in subjects with iron deficiency anemia in infancy. *Front Aging Neurosci*. 2017; 9:54.
23. Gogia S, Sachdev HS. Zinc supplementation for mental and motor development in children. *Cochrane Database Syst R*ev. 2012 Dec 12.12:CD007991.
24. Dror DK, Allen LH. Effect of vitamin B_{12} deficiency on neurodevelopment in infants: current knowledge and possible mechanisms. *Nutr* Rev. 2008; 66:250–255.
25. Srinivasan K, Thomas T, Kapenee ARM, Ramthal A, Bellinger DC, Bosch RJ, et al. Effects of maternal vitamin B_{12} supplementation on early infant neurocognitive outcomes: a randomized controlled clinical trial. *Matern Child Nutr*. 2017; 13:e12325.
26. Ars CL et al. Prenatal folate, homocysteine and vitamin B_{12} levels and child brain volumes, cognitive development and psychological functioning: the Generation R Study. *Br J N*utr. 2019 Sep;122(s1):S1-S9. doi: 10.1017/S0007114515002081.
27. Vandenplas Y et al. Human Milk Oligosaccharides: 2'-Fucosyllactose (2'-FL) and Lacto-N-Neotetraose (LNnT) in Infant Formula. *Nutrient*s. 2018 Aug 24;10(9). pii: E1161. doi: 10.3390/nu10091161.
28. Mosca, F.; Giannì, M.L. Human milk: Composition and health benefits. *Pediatr. Med. Chir*. 2017; 39, 155.
29. Donovan, S.M.; Comstock, S.S. Milk oligosaccharides influence neonatal mucosal and systemic immunity. *Ann. Nutr. Metab*. 2016; 69 (Suppl. 2), 42–51.
30. Austin, S.; De Castro, C.A.; Bénet, T.; Hou, Y.; Sun, H.; Thakkar, S.K.; Vinyes-Pares, G.; Zhang, Y.; Wang, P. Temporal change of the content of 10 oligosaccharides in the milk of Chinese urban mothers. *Nutrients* 2016;8, 346.
31. Hegar B et al. The Role of Two Human Milk Oligosaccharides, 2'-Fucosyllactose and Lacto-N-Neotetraose, in Infant Nutrition. *Pediatr Gastroenterol Hepatol Nutr*. 2019 Jul;22(4):330-340. doi: 10.5223/pghn.2019.22.4.330.
32. Jacobi SK, Yatsunenko T, Li D, Dasgupta S, Yu RK, Berg BM, et al. Dietary isomers of sialyllactose increase ganglioside sialic acid concentrations in the corpus callosum and cerebellum and modulate the colonic microbiota of formula-fed piglets. *J Nutr* 2016;146:200-8.
33. Tarr AJ, Galley JD, Fisher SE, Chichlowski M, Berg BM, Bailey MT. The prebiotics 3′Sialyllactose and 6′Sialyllactose diminish stressor-induced anxiety-like behavior and colonic microbiota alterations: evidence for effects on the gut-brain axis. Brain *Behav Immun* 2015;50:166-77.
34. Schneider N et al. Sphingomyelin in Brain and Cognitive Development: Preliminary Data. *eNeuro*. 2019 Aug 6;6(4). pii: ENEURO.0421-18.2019. doi: 10.1523/ENEURO.0421-18.2019.
35. Power VA et al. Nutrition, Growth, Brain Volume, and Neurodevelopment in Very Preterm Children. *J Pediatr.* 2019 Sep 24. pii: S0022-3476(19)31089-3. doi: 10.1016/j.jpeds.2019.08.031.
36. Hortensius LM et al. Postnatal Nutrition to Improve Brain Development in the Preterm Infant: A Systematic Review From Bench to Bedside. *Front Physiol*. 2019 Jul 26;10:961. doi: 10.3389/fphys.2019.00961. eCollection 2019.
37. Wang Q, Cui Q, Yan C. The Effect of supplementation of long-chain polyunsaturated fatty acids during lactation on neurodevelopmental outcomes of preterm infant from infancy to school age: a systematic review and meta-analysis. *Pediatr Neurol* 2016;59:54-61.e1.
38. Cormack BE et al. The Influence of Early Nutrition on Brain Growth and Neurodevelopment in Extremely Preterm Babies: A Narrative Review. *Nutrients*. 2019 Aug 30;11(9). pii: E2029. doi: 10.3390/nu11092029.
39. Cormack BE et al. The Influence of Early Nutrition on Brain Growth and Neurodevelopment in Extremely Preterm Babies: A Narrative Review. *Nutrients*. 2019 Aug 30;11(9). pii: E2029. doi: 10.3390/nu11092029.
40. Egan B et al. The effect of diet on the physical and mental development of children: views of parents and teachers in four European countries. *Br J Nutr*. 2019 Sep;122(s1):S31-S39. doi: 10.1017/S000711451500032X.

Infant Formula



Dietary Fatty Acids and Host-Microbial Crosstalk in Neonatal Enteric Infection[1]

Quin C, Gibson DL. Dietary Fatty Acids and Host-Microbial Crosstalk in Neonatal Enteric Infection. Nutrients. 2019 Sep 3;11(9). pii: E2064. doi: 10.3390/nu11092064.

In this review, Quin et al highlight the role of distinct types of dietary fatty acids in modulating host inflammation, both directly and through the gut microbiome and immunity. The authors present evidence that dietary fatty acids influence enteric disease susceptibility and, therefore, altering the fatty acid composition in formula may be a potential strategy to improve infectious outcomes in formula-fed infants.

The neonatal period represents a critical time in mammalian life, particularly with respect to nutritional programming of the gut microbiome and immunity required to respond to infectious diseases and chronic inflammatory conditions like allergies and autoimmune disease.

Human milk is the best nutritional choice for infants. However, in instances where breastfeeding is not possible, infant formulas are used as alternatives. A difficult challenge in mimicking the composition of breast milk derives from the complexities of breast milk itself. The composition of breast milk differs at various times of the day, throughout feeding, and at distinct stages of lactation.

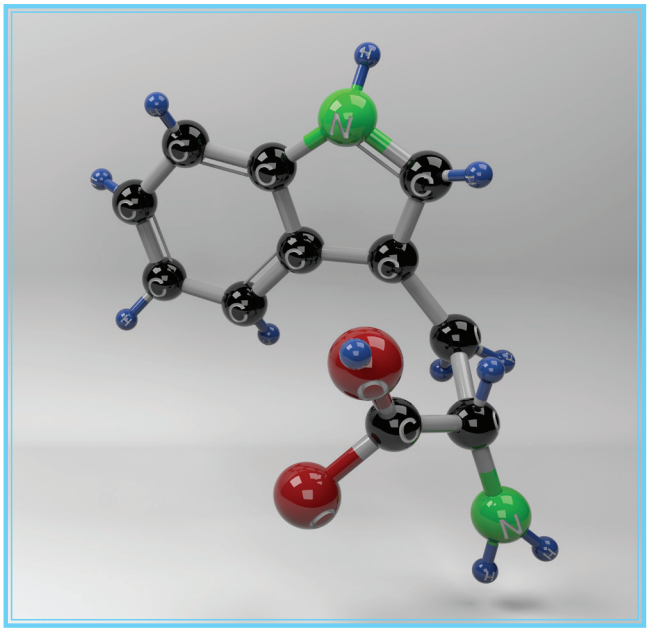
While formula manufacturers attempt to mimic the performance of human breast milk, it was shown that formula-fed babies consistently have higher incidences of infection from diarrheal diseases than those breastfed. Differences in disease susceptibility, progression and severity can be attributed, in part, to nutritional fatty acid differences between breast milk and formula. Despite advances in the understanding of breast milk properties, formulas still present major differences in their fatty acid composition when compared to human breast milk.

Recent studies have begun to appreciate that the saturation index between fatty acids has profound effects on

inflammation. In contrast, there is a large body of evidence showing that omega-3 polyunsaturated fatty acids have anti-inflammatory properties. Two polyunsaturated fatty acids, linoleic acid and alpha-linolenic acid are considered essential because they cannot be synthesized by the body. Current guidelines for the levels of polyunsaturated fats in infant formula aim to avoid a high linoleic (omega-6 polyunsaturated fatty acid) to alpha-linolenic (omega-3 polyunsaturated fatty acid) ratio, due to their pro-inflammatory functions. The consumption of omega-6 polyunsaturated fatty acid is associated with an increase in pro-inflammatory microbes and host-inflammatory mediators. Diets rich in omega-6 polyunsaturated fatty acids show robust inflammatory responses to enteric pathogens. While inflammation is required to survive infections, too much inflammation results in extensive host damage.

Long-chain omega-3 polyunsaturated fatty acids are considered beneficial to infant development. Most infant formula manufacturers now add manufactured eicosapentaenoic acid and docosahexaenoic acid to their product. However, several meta-analyses conclude that omega-3 polyunsaturated fatty acid supplements do not have an effect on infant visual acuity, memory, physical development, motor skills and cognition.

The functional outcomes of any differences in nutrition during infancy are still largely unknown. The microbiome plays a key role in the establishment of the immune system; however, the consequences of dietary fat-induced modifications to the microbial communities during infancy are still being investigated.



Optimized Protein Intakes in Term Infants Support Physiological Growth and Promote Long-Term health[2]

Koletzko B, Demmelmair H, Grote V, Totzauer M. Optimized protein intakes in term infants support physiological growth and promote long-term health. Semin Perinatol. 2019 Jun 22:151153. doi: 10.1053/j.semperi.2019.06.001.

It is well known that breastfeeding is associated with a reduced later obesity risk, relative to infant formula feeding. Breastfeeding induces less weight gain during the first two years of life, which predicts less obesity up to adulthood.

Koletzko et al tested the hypothesis that a high infant protein supply promotes weight gain and obesity risk, mediated by increased plasma amino acids and growth factors, insulin and insulin like growth factor 1 (IGF-1). The authors conducted a large multi-centre double blind trial comparing randomized formula fed infants to conventional bottle milk with a high protein content, or an intervention formula with a reduced protein content more similar to levels provided with human milk. Protein reduced formula normalized weight, body mass index (BMI) and body fatness up to 6 years, relative to a breastfed reference group, and reduced the adjusted odds for obesity 2,6 fold.

The authors concluded that infant feeding has very marked long-term programming effects on later BMI, obesity and adiposity, with major public health implications. As breastfeeding lowers the risk for later obesity and adiposity, it provides additional motivation for proactively and enthusiastically promoting, protecting and supporting breastfeeding. A high milk protein intake in infancy increases the long-term risk for obesity and adiposity. Infants not or not fully breastfed should receive infant formula delivering protein in amounts more similar to human milk contents, with high protein quality. It appears prudent to avoid other sources of very high protein intakes in infancy, in particular the use of cows' milk as a drink where feasible and affordable, since cows' milk contains three times as much protein as human milk.

Shorter Time to Full Preterm Feeding Using Intact Protein Formula: A Randomized Controlled Trial[3]

Baldassarre ME, Di Mauro A, Fanelli M, Capozza M, Wampler JL, Cooper T, Laforgia N. Int J Environ Res Public Health. 2019 Aug 14;16(16). pii: E2911. doi: 10.3390/ijerph16162911.

Meeting nutritional needs in the first weeks of life for preterm infants is a major clinical challenge within the neonatal intensive care unit (NICU) due to feeding intolerance. Baldassarre et al aimed to evaluate enteral feeding advancement and tolerance in preterm infants receiving one of two marketed formulas: intact protein preterm formula (IPF) or extensively hydrolyzed formula (EHF) for the first 14 feeding days.

In the current study, days to first achieving full enteral feedings (defined as a daily intake of ≥140 mL/kg/day) was the primary outcome variable compared in preterm infants receiving one of two isocaloric, marketed cow milk-based study formulas over the first 14 days of feeding. Per protocol analyses included the following: all participants who met study entrance criteria and completed study feeding (primary) and those who received ≥75% enteral intake from study formula (subset). Mothers were encouraged to provide their breast milk. The study enrolled participants who were randomized to intact protein preterm infant formula (IPF) or extensively hydrolyzed infant formula (EHF).

Of the 65 enrolled (IPF: n=32; EHF: n=33), 60 completed study feeding per protocol (IPF: n=30; EHF: n=30), 37 (62%) received predominantly breast milk, and 23 (38%) received ≥75% study formula intake (IPF: n=11; EHF: n=12). No group differences in tolerance measures were detected in this study. No necrotizing enterocolitis (NEC) was reported. The median time to achievement of full enteral feeding was significantly shorter for the IPF vs. EHF group (day 10 vs. 14, $p < 0.05$) (subset analysis). The mean enteral intake significantly increased by day 14 for the IPF group ($p < 0.05$), reflecting group divergence as achieved feeding volumes increased.

In conclusion, this pilot study demonstrated a statistically significant shorter time to full enteral feeding and higher achieved feeding volume by study end in preterm infants predominantly fed an intact protein preterm formula (IPF) compared to an extensively hydrolyzed infant formula (EHF) during the first 14 days of feeding. Current data suggest the continued use of IPF designed to meet the specific macro- and micro-nutrient needs of preterm infants when human milk is unavailable.

Human Milk Oligosaccharide Composition is Associated with Excessive Weight Gain During Exclusive Breastfeeding: An Explorative Study[4]

Larsson MW, Lind MV, Laursen RP, Yonemitsu C, Larnkjær A, Mølgaard C, Michaelsen KF, Bode L. Front Pediatr. 2019 Jul 18;7:297. doi: 10.3389/fped.2019.00297. eCollection 2019.

Some infants experience excessive weight gain during exclusive breastfeeding. The cause is unknown, but variation in human milk composition might play a role. Several human milk oligosaccharides (HMOs) have been associated with growth velocity in breastfed infants, and it has been suggested that the mechanism could be through an effect on infant gut microbiota composition.

In a small cohort, Larsson et al found significantly different HMO concentrations in milk to exclusively breastfed infants with excessive weight gain, suggesting that some HMOs, including 2'-fucosyllactose (2'-FL), which is the most abundant HMO and currently added to some

infant formula, could be part of the cause for the excessive weight gain.

The authors of the current study conducted this exploratory study aiming to evaluate if HMO composition was different in milk fed to infants with excessive weight gain compared to infants with normal weight gain. Moreover, they aimed to examine if HMO composition was associated with growth velocity and change in body composition and if there were maternal determinants of HMO composition. In light of this objective, they recruited 13 high weight-gain (HW) and 17 normal weight-gain (NW) breastfed infants, collected human milk and anthropometry data at 5 and 9 months, and analyzed HMO composition by high performance liquid chromatography.

In the HW group eight out of 11 infants received milk from secretor mothers and in the NW group 15 out of 17. Comparing milk from Secretor mothers only, the study findings revealed that four HMO's were significantly different between the HW and NW group at 5 months and two remained significant at 9 months. Total HMO concentrations as well as total HMO-bound fucose at 5 months were positively associated with both fat mass index (FMI) and weight velocity from 0 to 5 months (all $p<0.025$). 2'-fucosyllactose (2'-FL) was positively associated with weight velocity from 0 to 5 months and FMI at 5 months. In contrast, lacto-N-neotetraose was lower in the HW group ($p=0.012$) and negatively associated with height-for-age Z-scores ($p=0.008$), weight velocity from 0 to 5 months ($p=0.009$) and FMI ($p=0.033$). Maternal BMI at 5 months was negatively associated with 6'-sialyllactose and sialyl-lacto-N-tetraose (LSTb) and positively with 2'-FL, total HMO and total HMO-bound fucose (all $p\leq0.03$).

The current study demonstrated only borderline significant differences between the HW and NW groups in total HMO concentration and HMO diversity, indicating higher total HMO and lower diversity in the HW group. However, concentrations of several individual HMOs were significantly different between the two groups suggesting that the variation in HMO composition could be part of the explanation for the differences in growth between the two groups.

There is increasing interest in adding HMOs to infant formula in order to optimize the intestinal microbiota and the development of the immune system. Since HMOs might influence energy harvest through alterations of the microbiota, HMOs might also affect growth. The most plausible mechanism linking HMOs and growth is that HMOs play a role in developing the infant microbiome. Without being degraded by the infant digestive system, HMOs reach distal parts of the infant's intestine where they are metabolized by the intestinal microbiota further supported by the results showing that several HMOs were associated with anthropometry, growth velocity, and body composition in an analysis combining the HW and NW groups.

In conclusion, the authors found significant differences between HMO concentrations in a group of exclusively breastfed infants with high weight gain compared to a group of infants with normal weight gain, which emphasizes that HMOs play an important role in infant growth. h

Gastrointestinal Tolerance, Growth and Safety of a Partly Fermented Formula with Specific Prebiotics in Healthy Infants: A Double-Blind, Randomized, Controlled Trial[5]

Rodriguez-Herrera A, Mulder K, Bouritius H, Rubio R, Muñoz A, Agosti M, Lista G, Corvaglia L, Ludwig T, Abrahamse-Berkeveld M, Perez-Navero JL. Nutrients. 2019 Jul 5;11(7). pii: E1530. doi: 10.3390/nu11071530.

Over the past decades, several studies have indicated that (partly) fermented infant milk formulae beneficially impact gastrointestinal function. Fermentation processes using food-grade microorganisms generate bioactive compounds, which are also known as postbiotics. Specific postbiotics are reported to have antimicrobial, antioxidative and immunomodulatory properties.

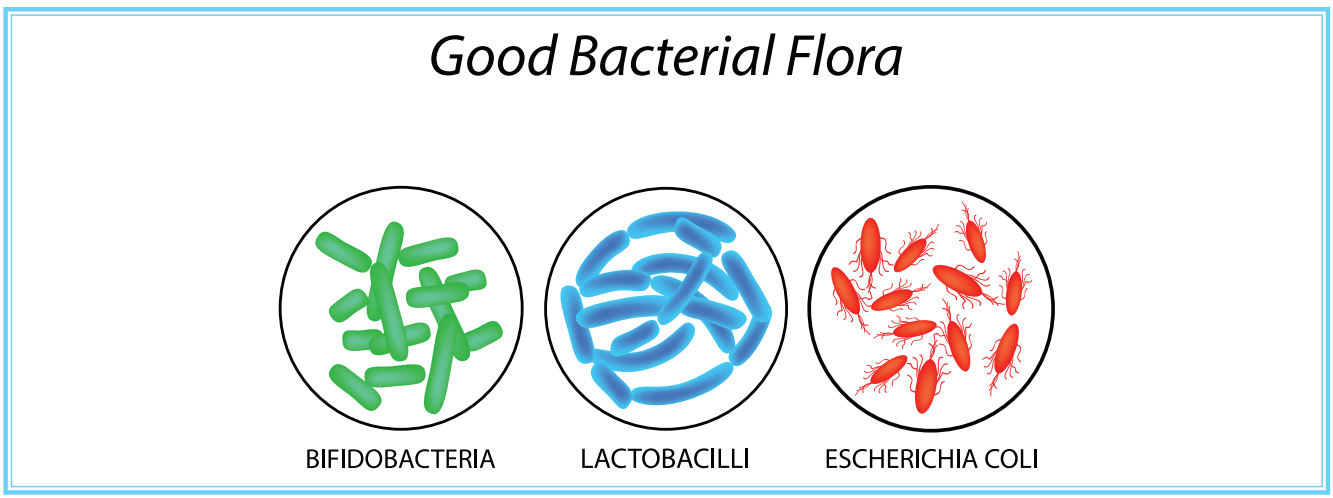
In the double-blind, randomized, controlled explorative study, Rodriguez et al evaluated the effect of a partly fermented infant formula (using the bacterial strains *Bifidobacterium breve* C50 and *Streptococcus thermophilus* 065) with a specific prebiotic mixture (short-chain galacto-oligosaccharides (scGOS) and long-chain fructo-oligosaccharides (lcFOS; 9:1)) on the incidence of gastrointestinal symptoms, stool characteristics, sleeping and crying behavior, growth adequacy and safety.

Two-hundred infants ≤28 days of age were assigned either to experimental infant formula containing 30% fermented formula and 0.8 g/100 mL scGOS/lcFOS or to non-fermented control infant formula without scGOS/lcFOS. A group of breastfed infants served as a reference.

The authors found no relevant differences in parent-reported gastrointestinal symptoms. Stool consistency was softer in the experimental versus control group with values closer to the breastfed reference group. Daily weight gain was equivalent for both formula groups (0.5 SD margins) with growth outcomes close to breastfed infants. No clinically relevant differences in adverse events were observed, apart from a lower investigator-reported prevalence of infantile colic in the experimental versus control group (1.1% vs. 8.7%; $p<0.02$). Both study formulae were well-tolerated, supported an adequate infant growth and were safe for use in healthy term infants. In comparison to the control formula, the researchers found that the partly fermented formula with prebiotics induced stool consistencies closer to breastfed infants.

In approximately 85% of the infants, irrespective of infant feeding, at least one occasion of aGI symptom was reported by parents or caregivers as moderate to severe. This is in line with the fact that GI symptoms are known to appear in a significant proportion of infants during the first 6 to 12 months.

The prebiotic mixture scGOS/lcFOS (9:1) present in the experimental formula, has been shown to stimulate the intestinal colonization with bifidobacterial, which results in beneficial effects on immune function and has a stool softening effect. The daily dairies of the current study resulted in >40.000 individual observations for stool characteristics (as well as on crying and sleeping behavior) of formula and breastfed infant, potentially providing the most extensive reference in the field.



Ketogenic Diet & Epilepsy

The ketogenic Diet in Children 3 Years of Age or Younger: a 10-Year Single-Center Experience[6]

Kim SH, Shaw A, Blackford R, Lowman W, Laux LC, Millichap JJ, Nordli DR Jr. Sci Rep. 2019 Jun 19;9(1):8736. doi: 10.1038/s41598-019-45147-6.

The ketogenic diet (KD) is a high fat, low carbohydrate, and protein restricted diet that is rigorously medically supervised and widely recognized as an effective treatment option for intractable epilepsy. Overall, while the KD's use as a therapy for infantile spasms (IS) is perhaps the best known and investigated, its effectiveness, safety, and tolerability for infantile onset intractable epilepsy regardless of seizure type has started to be elaborated.

In this study, Kim SH et al analyzed the last 10 years of their experience with the KD and characterized its use in patients under 3 years of age. Medical records of all patients under the age of 3 years who were treated with the ketogenic diet from April 2004 to June 2014 were retrospectively reviewed. The authors aimed to (1) identify predictors of favorable outcome, (2) investigate reasons for early withdrawal with relation to age, diet formulation, or adverse events, and (3) evaluate the efficacy with specific regard to epilepsy syndrome or etiology, utilizing genetic diagnoses if available.

In light of these goals, one hundred and nine patients with drug-resistant epilepsy were included. The mean age at the initiation of the KD was 1.4 ± 0.8 years old. The youngest patient was 3 weeks old. After 3 months, 39% (42/109) of patients responded to the KD and experienced more than 50% seizure reduction. Of those 42 patients, 20 (18%) achieved complete seizure control. Patients with a genetic etiology showed a better response to the KD in seizure reduction than the other patients ($p = 0.03$). Age at initiation

of the KD was not related to eventual seizure outcome ($p = 0.6$).

Within a span of 10 years in author's center, more than 100 patients were initiated on the KD before they turned 3 years old. Overall, 20% of patients became seizure free and many (39%) experienced a significant seizure reduction (>50%) after the initial 3-months of the KD therapy. This trend is similar to what other studies have reported for older children, in which 27–38% of children have a >50% seizure reduction after 3 months.

Based on authors' experience, a confirmed genetic abnormality was predictive of a good response to the KD. Nearly half of the patients with a confirmed genetic abnormality enjoyed a reduction in seizure frequency of >50%. A similar finding was described in a retrospective chart review of 64 consecutive patients with refractory epilepsy, children and adults, who were started on the KD at a tertiary epilepsy center. This finding implies that the KD could also be considered by providers earlier, perhaps even before a patient fails two previous anticonvulsant medications, if he or she receives a positive genetic diagnosis.

In this study, age was not related to the seizure outcome but to the methods of the KD and to the adverse events. Younger ones (<1 year old) were more likely to be fed with the liquid KD food, while older ones (>2 years old) were fed with the solid foods.

In conclusion, KD continues to be an effective, safe, and well tolerated treatment option for infants with intractable epilepsy. Tolerability may be enhanced by using a liquid-based diet in this age group, the role of expressed breast milk in which should be further elaborated. The availability of new diagnostic studies such as genetic testing could promote early and effective use of the KD by identifying patients who might favorably respond to the KD.

Initiating the Ketogenic Diet in Infants with Treatment Refractory Epilepsy While Maintaining a Breast Milk Diet[7]

Le Pichon JB, Thompson L, Gustafson M, Abdelmoity A. Seizure. 2019 Jul;69:41–43. doi: 10.1016/j.seizure.2019.03.017.

Neonatal epilepsy remains a significant problem. Several large prospective studies have shown that up to 38% of infants with epilepsy were classified as drug resistant epilepsies. Furthermore, the outcome for these infants remains rather poor, with 17% dying and 49% having an abnormal exam at the time of discharge. Until recently there were no guidelines for the treatment of seizures in the newborn.

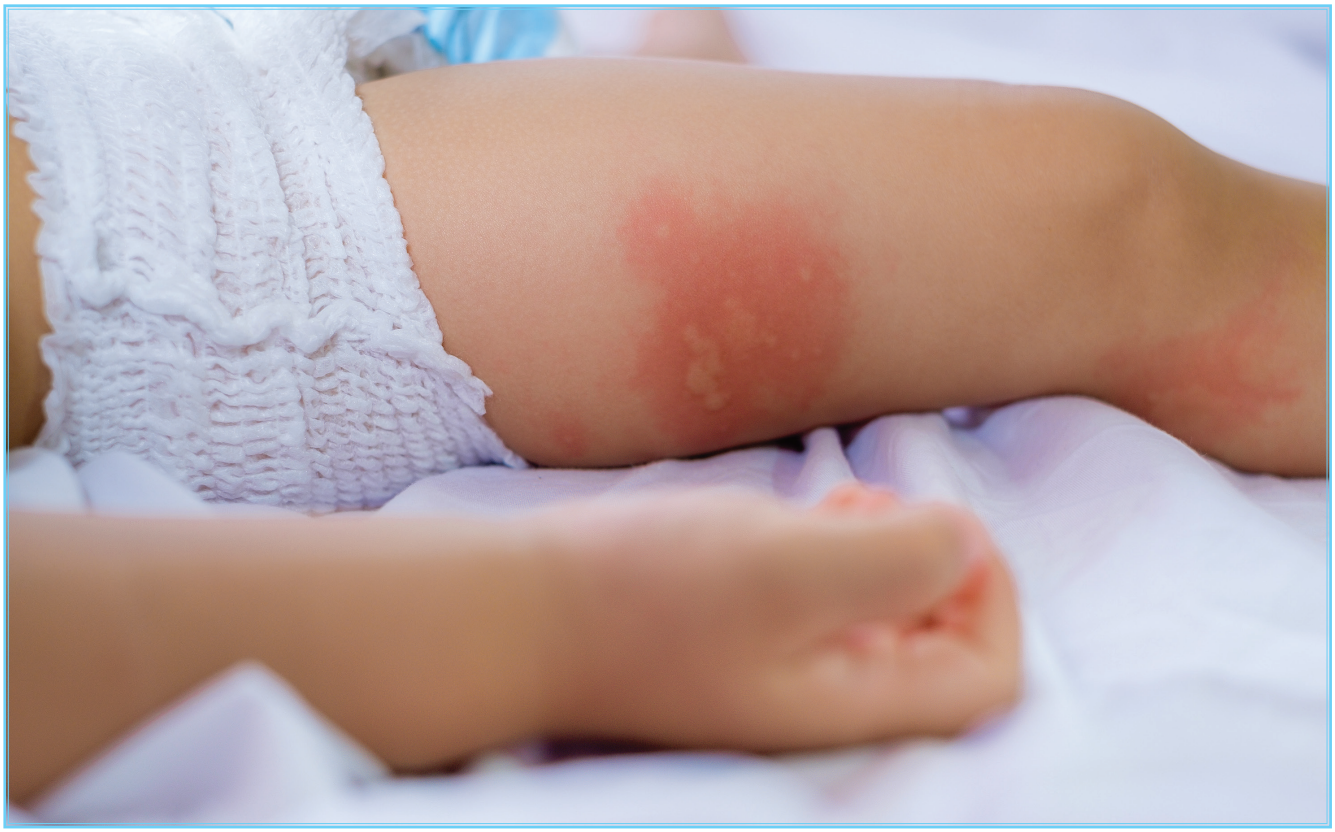
The ketogenic diet has been found to be safe and effective in the treatment of drug resistant epilepsy in childhood. The age range of children undergoing this treatment has steadily been going down. There is strong evidence that it is a safe alternative in infants with drug resistant seizures. The American Academy of Pediatrics strongly supports continuing a breast milk diet until infants are at least six months of age.

Le Pichon et al conducted a study of infants who received ketogenic diet therapy in the Comprehensive Epilepsy Center at Children's Mercy Hospital between May 2005 and January 2016. The purpose of this study was to evaluate the safety and efficacy of the ketogenic diet in infants while maintaining a breast milk diet. In this cohort study, 9 infants between the ages of 1 and 13 months with drug resistant epilepsy were treated with the ketogenic diet while maintained on breast milk. The data from the first two patients was gathered retrospectively while the other seven were studied prospectively.

The authors showed that all nine infants achieved and maintained ketosis effectively. While one infant had no change in seizure frequency, three were seizure free at the first follow-up visit and four had a burden of seizure reduction greater than 50%. The diet was overall well tolerated, although one child required a hospital stay for dehydration and metabolic acidosis. All of the infants achieved ketosis prior to discharge (as measured by urine ketones and serum beta-hydroxybutyrate levels) and maintained ketosis (as measured by serum beta-hydroxybutyrate levels) at subsequent visits.

The authors concluded that the ketogenic diet can be safely and effectively initiated in infants while continuing human breast milk feedings. Given the American Academy of Pediatrics' strong endorsement of breast-feeding infants and given the increased use of the ketogenic diet to treat drug resistant epilepsy in infants, finding a solution that allows for maintenance of a diet of breast milk while on the ketogenic diet is of importance.

Cow's Milk Allergies



An Update to the Milk Allergy in Primary Care Guideline[8]

Fox A, Brown T, Walsh J, Venter C, Meyer R, Nowak-Wegrzyn A, Levin M, Spawls H, Beatson, Lovis MT, Vieira MC, Fleischer D. Clin Transl Allergy. 2019 Aug 12;9:40. doi: 10.1186/s13601-019-0281-8. eCollection 2019.

The Milk Allergy in Primary (MAP) Care guideline was first published in 2013 in *Clin. Transl. Allergy* journal. MAP aimed to provide simple and accessible algorithms for UK clinicians in primary care, detailing all the steps between initial presentation, through diagnosis, management and tolerance development. In healthcare environments where there is minimal specialist allergy provision, it remains important that mild-moderate non-IgE mediated cow's milk allergy (CMA) can be diagnosed accurately and promptly in the primary care setting where these infants are most likely to present.

Despite its UK focus, it soon became clear that MAP was being accessed internationally and thus an updated International Milk Allergy in Primary Care (iMAP) guideline was published in 2017. Both guidelines used existing International consensus guidelines to develop accessible algorithms accompanied by patient information leaflets.

In 2018, the guidelines were criticized for 3 distinct reasons: promoting the overdiagnosis of cow's milk allergy (CMA), negatively impacting breastfeeding and the possibility of industry influence on the guidelines.

The authors addressed these criticisms using available evidence and, in the context of this and in consultation with

patient groups, members of the General Practice Infant Feeding Network and other infant feeding healthcare leads, have collaboratively produced updated algorithms and an information leaflet to support breastfeeding.

Whilst the authors did not agree that either MAP or other guidelines have driven the increased prescriptions of hypoallergenic formulas, they acknowledged that the symptoms of mild to moderate non-IgE mediated CMA overlapped significantly with a large number of completely well infants. They emphasized the fact that patients are protected from unnecessary diagnostic elimination diet trials.

The authors importantly noted that one of the most likely causes of overdiagnosis is misclassification of patients as being allergic, due to failure to conduct a re-challenge to milk after a brief exclusion. Without confirming that symptoms return on reintroduction of milk following a diagnostic elimination diet trial, only a presumptive diagnosis of CMA can be made, and there is a risk that infants whose symptoms in fact resolved spontaneously, and not as a result of milk exclusion, will be wrongly labelled as milk-allergic.

The authors believe iMAP is closer to its original aim of facilitating early and accurate diagnosis of CMA, whilst minimizing, as far as possible, any concerns around overdiagnosis or a risk to breastfeeding rates. They continue to welcome open and constructive engagement about how best to achieve these aims to provide evidence-based, practical guidelines for the primary care practitioner.

The Potential for Pre-, Pro- and Synbiotics in the Management of Infants at Risk of Cow's Milk Allergy or with Cow's Milk Allergy: An Exploration of the Rationale, Available Evidence and Remaining Questions[9]

Fox A, Bird JA, Fiocchi A, Knol J, Meyer R, Salminen S, Sitang G, Szajewska H, Papadopoulos N. World Allergy Organ J. 2019 Jun 4;12(5):100034. doi: 10.1016/j.waojou.2019.100034. eCollection 2019.

Cow's milk allergy is one of the most commonly reported childhood food allergies, with increasing incidence, persistence and severity in many countries across the world. The World Allergy Organization Special Committee on Food Allergy has identified cow's milk allergy as an area in need of a rationale-based approach in order to make progress against what it considered an onerous problem, with worldwide public health impact. There is growing interest in the potential role of the gut microbiota in the early programming and development of immune responses and allergy.

This discussion paper considers the rationale and available evidence for modulation of the gut microbiota and for the use of synbiotics in the management of infants at risk of, or living with cow's milk allergy (CMA) and summarizes remaining research questions that need to be answered for the development of evidence-based recommendations.

Currently available evidence does not indicate that probiotic supplementation reduces the risk of any allergic manifestation in children. However, considering all critical outcomes including efficacy, safety and tolerability data in this context, the World Allergy Organization (WAO) guideline panel stated 'that there is a likely net benefit from using probiotics resulting primarily from prevention of eczema.

Currently, guidelines do not make specific recommendations on the use of probiotics and prebiotics in the treatment of CMA because of a lack of evidence at the time they were developed. The WAO guidelines considered modulation of the immune system using functional foods offers a promising research hypothesis as part of efforts to induce a tolerogenic immune environment in the context of CMA.

Clearer definitions and signatures of healthy and allergy microbiomes are needed, taking into account that these will vary in different parts of the world, across different categories of risk, and in different social classes.

Understanding complex diseases such as allergies, including CMA, is challenging with multiple risk factors and mechanisms occurring and interacting at the same time. Research methods, such as bioinformatics approaches, are being developed to assess this multi-causality and complexity but more work is needed.

Influence of Prenatal and Early-Life Exposures on Food Allergy and Eczema in Infancy: A Birth Cohort Study[10]

Gao X, Yan Y, Zeng G, Sha T, Liu S, He Q, Chen C, Li L, Xiang S, Li H, Tan S, Yan Q. BMC Pediatr. 2019 Jul 17;19(1):239. doi: 10.1186/s12887-019-1623-3.

This study, conducted by Gao et al, suggests that factors associated with food allergy and eczema are multifaceted, involving hereditary, environmental and nutritional exposures. Moreover, the authors emphasize the fact that differential factors influence the development of food allergy and eczema in infants.

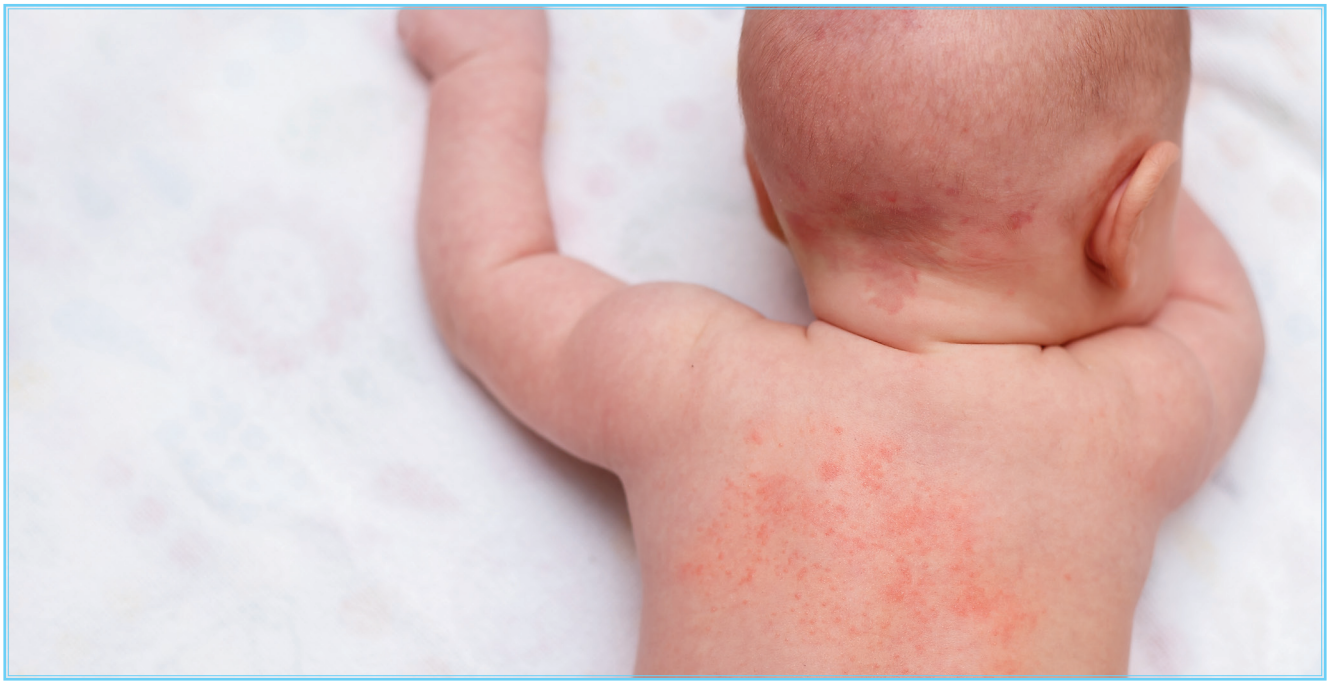
Food allergy and eczema often begin to appear very early in life, which implies that genetic predisposition, as well as prenatal and early childhood exposures might influence the development of these allergic outcomes. Few prospective birth cohort studies are available on the effects of prenatal and early-life exposures on food allergy and eczema among Chinese children. The aim of this study was to evaluate the influence of prenatal and early-life exposures on food allergy and eczema during the first year of life in a prospective birth cohort study.

This study was conducted on the basis of a prospective, observational birth cohort of 976 mother-child pairs in three Streets in Changsha, China from January to December 2015. Data on prenatal, early-life exposures and allergic outcomes were obtained from questionnaires collected at birth, and 1, 3, 6, 8, and 12 months of age. Multivariate logistic regression models were performed to estimate the effects of prenatal and early-life exposures on food allergy and eczema.

The authors found that common risk factors for food allergy and eczema in infancy were parental history of allergy, while moderate eggs consumption (3-4 times/week) during pregnancy was protective for both of them compared with low consumption (≤ 2 times/week). Factors only associated with food allergy were maternal aquatic products consumption during pregnancy, number of older siblings and age of solid food introduction, whereas factors only associated with eczema were maternal milk or milk products consumption during pregnancy, maternal antibiotic exposure during pregnancy, season of birth and antibiotic exposure through medication during the first year of life.

Food allergy and eczema often begin to appear very early in life, which implies that genetic predisposition, as well as prenatal and early childhood exposures might influence the development of these allergic outcomes.

Identifying the risk and protective factors for food allergy and eczema may help to develop specific and early preventative measures and to reduce the prevalence of food allergy and eczema, even that of allergic diseases.



Gastrointestinal Disorders

Neonatal Antibiotics and Prematurity are Associated with an Increased Risk of Functional Gastrointestinal Disorders in the First Year of Life[11]

Salvatore S, Baldassarre ME, Di Mauro A, et al J Pediatr. 2019 Sep;212:44-51. doi: 10.1016/j.jpeds.2019.04.061.

Functional gastrointestinal disorders (FGIDs) include a variable combination of chronic or recurrent gastrointestinal symptoms in the absence of structural or biochemical abnormalities. Despite heterogeneity in methods and definitions, many infants <12 months are affected by FGIDs, with a reported overall prevalence of 50% in newborns born full term and up to 73% with infantile colic and 87% with regurgitation in selected population.

The 2006 Rome III criteria classified and clinically distinguished different FGIDs, in neonates and toddlers, including infant regurgitation, infant rumination syndrome, cycling vomiting syndrome, infant colic, functional diarrhea, infant dyschezia, and functional constipation.

There is evidence that early life events play a pivotal role in the programming of different diseases later in life. Some authors speculated that the type of delivery, feeding practice, and early antibiotic administration may predispose infants to FGIDs.

In this study, Salvatore et al aimed to assess the prevalence of FGIDs in the first year of life and the influence of different neonatal factors on development of FGIDs. In light of this objective, this prospective cohort multicenter study enrolled neonates at birth, followed up until 1 year. Gestational age, neonatal antibiotic administration, duration of hospitalization, mode of delivery, birth weight, and feeding pattern were recorded. FGIDs were classified according to Rome III criteria and assessed at 1, 3, 6, and 12 months of life.

According to the authors' findings, among 1152 newborns enrolled, 934 (81.1%) completed the study, 302 (32%) were

newborns born preterm, 320 (34%) had neonatal antibiotics, and 718 (76.9%) had at least 1 FGID according to Rome III criteria (443 [47.4%] infantile colic, 374 [40.0%] regurgitation, 297 [31.8%] infant dyschezia, 248 [26.6%] functional constipation, and 34 [3.6%] functional diarrhea) throughout the first year of life. The proportion of infants born preterm presenting with FGIDs (86%) was significantly greater compared with infants born full term (72.5%) (χ^2=21.3, p=0.0001). On multivariate analysis, prematurity and neonatal use of antibiotics was significantly associated with at least 1 FGID.

The diagnosis of FGIDs relies on clinical criteria, with exclusion of warning signs for organic diseases, because specific biomarkers or investigation are still lacking. Rome III and, more recently, Rome IV criteria provide a detailed classification of different FGIDs at different ages. However, a heterogeneity of diagnosis or misclassification among different physicians and an overestimation of prevalence of FGIDs cannot be excluded.

Recognition of the exact prevalence of FGIDs is important to plan a tailored program of parents' education and clinical follow-up. Moreover, identification of associated neonatal risk factors for FGIDs represents an essential prerequisite to develop possible early life interventions to decrease FGIDs later in life.

By analyzing their results, the authors point out that in case of data confirmation, a balanced strategy to reduce unnecessary neonatal antibiotic use and to promote intestinal homeostasis in at risk neonates should be considered. Nonetheless, parental education and reassurance on FGIDs and appropriate nutritional advice by healthcare professionals could reduce the inappropriate use of medication or dietary interventions later in life.

In conclusion, the authors found a high rate FGIDs in infants, likely related to the population recruited, the long observation period, the diagnosis based on Rome III criteria, and parental reports. Preterm delivery and neonatal use of antibiotics in the first months of life are associated with an increased incidence of FGIDs, particularly infantile colic and regurgitation. In this population, cesarean delivery and feeding pattern at 1 month of life emerged as additional risk factors for infant dyschezia and functional diarrhea. Other neonatal factors associated with FGIDs need to be further explored.

Metabolic Disorders

Common Metabolic Disorder (Inborn Errors of Metabolism) Concerns in Primary Care Practice[12]

Marisha Agana et al. Ann Transl Med. 2018 Dec; 6(24): 469. doi: 10.21037/atm.2018.12.34

Inborn errors of metabolism (IEMs) are rare genetic or inherited disorders resulting from an enzyme defect in biochemical and metabolic pathways affecting proteins, fats, carbohydrates metabolism or impaired organelle function presenting as complicated medical conditions involving several human organ systems. They involve great complexity of the underlying pathophysiology, biochemical workup, and molecular analysis, and have complicated therapeutic options for management.

Children and adolescents with IEMs have a wide spectrum of clinical presentations from appearing physically normal to having distinctive dysmorphic physical features. While majority of them appear physically normal at birth, many can present with significant non-specific signs and symptoms common to other serious medical conditions. It is imperative to keep a high index of suspicion in differential diagnosis for prompt IEM identification as the institution of appropriate therapy, preventive measures and compliance helps avoid severe morbidity or even mortality in some cases.

Age of presentation can vary from infancy to adolescence with the more severe forms appearing in early childhood accompanied by significant morbidity and mortality. The understanding of these complex disorders requires special in-depth training, American Board of Medical Genetics and Genomics (ABMGG) certification and experience.

Infants, children and adolescents with IEM who appear normal may succumb to life-threatening conditions. Appropriate acute illness protocol and specific supportive

therapies are needed to assure the patient's survival. Many patients will require respiratory and circulatory support. Most will require rehydration, correction of electrolyte imbalance and even treatment of overwhelming infection from opportunistic organisms that uncorrected can lead to persistent catabolic state and failure of definitive therapeutic intervention.

Most primary care physicians (PCPs) are reluctant to deal with IEM due to unfamiliarity and rarity of such conditions compounded by prompt progression to crisis situations along with paucity of time involved in dealing with such complex disorders. While there are biochemical geneticists and metabolic specialists' expertise available, mostly in larger academic medical centers, with expertise to deal with these rare complex issues, their initial clinical presentation in most newborns, children, adolescents or adults including asymptomatic positive newborn screen (NBS), occur in the out-patient PCP settings. Therefore, it is important that PCPs' comfort to recognize early signs and symptoms is important to initiate appropriate diagnostic and therapeutic interventions, and be able to make appropriate referrals.

Addressing the nutritional requirements of the patient is very important, whatever the IEM disease condition. Total parenteral nutrition (TPN) is the preferred choice in those cases wherein effective enteral nutrition is not acceptable due to intestinal intolerance, high energy or high glucose requirements or the introduction of invasive techniques are needed for immediate detoxification.

In this review, the authors analyzed common IEM clinical presentations for a robust diagnostic differential and discussed evaluation and management approaches of patients with known or suspected IEM.

Maternal Microbiome and Metabolic Health Program Microbiome Development and Health of the Offspring[13]

Calatayud , Koren O, Collado MC. Trends Endocrinol Metab. 2019 Sep 4. pii: S1043-2760(19)30156-0. doi: 10.1016/j.tem.2019.07.021.

Maternal nutritional, metabolic, and physiological states, as well as exposure to various environmental factors during

conception, gestation, and lactation, have a fundamental role in the health programming of the offspring. Therefore, alterations affecting the maternal microbiota might indirectly influence fetal development. In addition, such alterations could be transmitted to the progeny at different stages of infant development (e.g., preconception, prenatal, or postnatal), thereby favoring the development of an altered microbiota in the neonate.

During breastfeeding, the neonate's microbiome evolves and becomes more diverse and complex; following the introduction of food, it shifts to an adult-type microbiome at between 2 and 4 years of age. The key factor shaping neonatal microbiota development is the mother's breastfeeding status, whether exclusive or partial. Furthermore, the mode of birth, as well as the adopted breastfeeding practices and antibiotic treatment during the first 2 years of life, have been found to be associated with a distinct oral and gut bacterial composition at a later age.

The gut microbiota may contribute to gestational metabolic changes, although the exact mechanisms behind this contribution remain unknown. Furthermore, it has been suggested that multiple childhood difficulties (e.g., chronic

stress or abuse) program an exaggerated adult inflammatory response to stress, thereby driving changes in the gut microbiota during pregnancy.

The delivery mode, nutritional status of the mother, and perinatal environmental exposures all impact the gut microbiota, thereby affecting the nutritional and metabolic status of the host.

Maternal metabolic status and diet during pregnancy have a key impact on both the maternal and infant microbiota, although the detailed effects remain obscure.

Microbial changes have been linked to an increased risk of non-communicable diseases (NCDs), including obesity and metabolic syndrome, allergy-related problems, and diabetes.

In this review, the authors summarized the relevance of the maternal microbiota to fetal-neonatal health programming, with a focus on maternal nutritional and metabolic states.

Association Between Pre-Pregnancy Body Weight and Dietary Pattern with Large-for-Gestational-Age Infants in Gestational Diabetes[14]

Munda A, Starčič Erjavec M, Molan K, Ambrožič Avguštin J, Žgur-Bertok D, Pongrac Barlovič D. Diabetol Metab Syndr. 2019 Aug 22;11:68. doi: 10.1186/s13098-019-0463-5. eCollection 2019.

The epidemic of obesity and the growing incidence of diabetes are global public health issues. Obesity affects both sexes and all age groups. On a global scale, in 2016 40% of women and 39% of men were overweight, while 11% of men and 15% of women were obese. Excessive weight and obesity are also increasing among children and adolescents with and 18% prevalence of obesity among the 5 to 19 year age group. Both obesity and gestational diabetes (GDM) are associated with adverse outcomes. Diet during pregnancy impacts weight gain and fetal growth.

GDM treatment is usually focused on nutrition and/or physical activity with many times inconsistent results. This may be because often glycemic control is overemphasized compared to the effects of obesity or gestational weight gain on negative pregnancy outcomes in everyday clinical practice.

In this study, Munda et al, aimed to explore non-pharmacological treatment success depending on pre-pregnancy body weight and its association with large for gestational age (LGA) infants in women with GDM. In light of this objective, they conducted an observational study and investigated 57 singleton pregnant women with GDM. All women received standard treatment, including healthy diet education and regular medical checkups. Data were collected through blood analysis, medical records and questionnaires assessing diet before conception and during pregnancy. Differences in dietary patterns were compared in normal weight and overweight/obese group using Mann-Whitney U, Wilcoxon Signed Rank Test or Kruskal-Wallis test, as appropriate. Logistic regression was used for prediction of LGA. p-value less than 0.05 was used for statistical significance.

Preconceptionally, the Mann-Whitney U test showed that the normal-weight group (n = 41) more frequently consumed fruits ($U = 116.5, p < 0.001$), eggs ($U = 189.5, p = 0.02$), cheese ($U = 148.0, p = 0.003$) compared to the overweight/obese group (n = 16), that consumed more beef ($U = 407.0, p = 0.03$) and low-calorie beverages ($U = 397.0, p = 0.05$). During pregnancy both groups improved their diet, with no differences detected. Personality types differed only preconceptionally with regard to healthy diet. Excessive gestational weight gain did not significantly differ between body-weight groups (16.6% vs. 23.1%), neither did the incidence of LGA infants (46.2% vs. 43.8%). Significant predictors of LGA were paternal height (OR = 1.12, 95% CI 1.01-1.23), 3rd trimester HbA1c (OR = 0.50, 95% CI 0.26-0.97), unemployment (OR = 4.80, 95% CI 1.12-20.61) and diet improvement during pregnancy (OR = 1.19, 95% CI 1.02-1.39). After adjustment improvement in diet was no longer a significant predictor for LGA.

The authors showed that preconception diet disparities among normal weight and overweight/obese groups and among different personality types disappeared during pregnancy. Women improved their dietary patterns, independently of obesity status or personality type, thereby confirming the success of education and non-pharmacological treatment of GDM. Excessive gestational weight gain did not significantly differ between the BMI groups; neither did the incidence of LGA infants.

Unexpectedly, disparities among BMI groups preconception regarding the healthy diet score were not found in

this study. Both groups followed the healthy diet guidelines. In addition, a positive association between BMI and fried food consumption was expected. However, a negative correlation was found, especially among overweight/obese women.

In this study infrequent consumption of fruits, eggs and cheese at baseline contributed to higher BMI pre-conception. Compared to the normal weight group, overweight/obese women more often consumed milk and beef before pregnancy.

Despite the fact that only a minority of women exceeded the recommended gestational weight gain and that all exhibited good glycemic control, the prevalence of LGA newborns in our study was relatively high. Interventions could help to limit weight gain.

The authors concluded that even though dietary patterns of the participants significantly improved during pregnancy, LGA infants were born independently of pre-pregnancy weight or diet and despite good glycemic control. Further research is needed to explore social determinants of health and whether solutions outside the health sector could provide efficient means in preventing adverse pregnancy outcomes as well as improving metabolic health.

Developmental Undernutrition and Obesity and Type 2 Diabetes in Offspring[15]

Perng W, Oken E, Dabelea D. Diabetologia. 2019 Oct;62(10):1779-1788. doi: 10.1007/s00125-019-4914-1.

Childhood obesity has reached pandemic proportions, and youth-onset type 2 diabetes is following suit. It is of interest in public health to establish the magnitude of the risk of cardiometabolic disease that individuals exposed to mismatch carry with them, in order to develop effective intervention strategies to mitigate later adverse outcomes.

This review summarizes the literature on the influence of developmental overnutrition, resulting from maternal diabetes, obesity, maternal dietary intake during pregnancy, excess gestational weight gain, and infant feeding practices, on the aetiology of obesity and type 2 diabetes risk during childhood and adolescence. Perng et al, address the challenges inherent in the study of the long-term consequences of nutritional exposure in fetal life and early childhood.

The key goals of this review were: (1) to summarize evidence to date on consequences of developmental overnutrition; (2) to describe shared and distinct biological pathways that may link developmental overnutrition to childhood obesity and youth-onset type 2 diabetes; and (3) to translate current knowledge into clinical and public health strategies that not only target primary prevention in youth, but also encourage primordial prevention during the perinatal period, with the aim of breaking the intergenerational cycle of obesity and diabetes.

References

1. Quin C, Gibson DL. Dietary Fatty Acids and Host-Microbial Crosstalk in Neonatal Enteric Infection. Nutrients. 2019 Sep 3;11(9). pii: E2064. doi: 10.3390/nu11092064.
2. Koletzko B, Demmelmair H, Grote V, Totzauer M. Optimized protein intakes in term infants support physiological growth and promote long-term health. Semin Perinatol. 2019 Jun 22:151153. doi: 10.1053/j.semperi.2019.06.001.
3. Baldassarre ME, Di Mauro A, Fanelli M, Capozza M, Wampler JL, Cooper T, Laforgia N. Int J Environ Res Public Health. 2019 Aug 14;16(16). pii: E2911. doi: 10.3390/ijerph16162911.
4. Larsson MW, Lind MV, Laursen RP, Yonemitsu C, Larnkjær A, Mølgaard C, Michaelsen KF, Bode L. Front Pediatr. 2019 Jul 18;7:297. doi: 10.3389/fped.2019.00297. eCollection 2019.
5. Rodriguez-Herrera A, Mulder K, Bouritius H, Rubio R, Muñoz A, Agosti M, Lista G, Corvaglia L, Ludwig T, Abrahamse-Berkeveld M, Perez-Navero JL. Nutrients. 2019 Jul 5;11(7). pii: E1530. doi: 10.3390/nu11071530.
6. Kim SH, Shaw A, Blackford R, Lowman W, Laux LC, Millichap JJ, Nordli DR Jr. Sci Rep. 2019 Jun 19;9(1):8736. doi: 10.1038/s41598-019-45147-6.
7. Le Pichon JB, Thompson L, Gustafson M, Abdelmoity A. Seizure. 2019 Jul;69:41-43. doi: 10.1016/j.seizure.2019.03.017.
8. Fox A, Brown T, Walsh J, Venter C, Meyer R, Nowak-Wegrzyn A, Levin M, Spawls H, Beatson, Lovis MT, Vieira MC, Fleischer D. Clin Transl Allergy. 2019 Aug 12;9:40. doi: 10.1186/s13601-019-0281-8. eCollection 2019.
9. Fox A, Bird JA, Fiocchi A, Knol J, Meyer R, Salminen S, Sitang G, Szajewska H, Papadopoulos N. World Allergy Organ J. 2019 Jun 4;12(5):100034. doi: 10.1016/j.waojou.2019.100034. eCollection 2019.
10. Gao X, Yan Y, Zeng G, Sha T, Liu S, He Q, Chen C, Li L, Xiang S, Li H, Tan S, Yan Q. BMC Pediatr. 2019 Jul 17;19(1):239. doi: 10.1186/s12887-019-1623-3.
11. Salvatore S, Baldassarre ME, Di Mauro A, et al J Pediatr. 2019 Sep;212:44-51. doi: 10.1016/j.jpeds.2019.04.061.
12. Marisha Agana et al. Ann Transl Med. 2018 Dec; 6(24): 469. doi: 10.21037/atm.2018.12.34
13. Calatayud , Koren O, Collado MC. Trends Endocrinol Metab. 2019 Sep 4. pii: S1043-2760(19)30156-0. doi: 10.1016/j.tem.2019.07.021.
14. Munda A, Starčič Erjavec M, Molan K, Ambrožič Avguštin J, Žgur-Bertok D, Pongrac Barlovič D. Diabetol Metab Syndr. 2019 Aug 22;11:68. doi: 10.1186/s13098-019-0463-5. eCollection 2019.
15. Perng W, Oken E, Dabelea D. Diabetologia. 2019 Oct;62(10):1779-1788. doi: 10.1007/s00125-019-4914-1.