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REVIEW

Nutrition and neurodevelopment in children: focus on NUTRIMENTHE project

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Abstract There is growing evidence that early nutrition affects later cognitive performance. The idea that the diet of mothers, infants, and children could affect later mental performance has major implications for public health practice and policy development and for our understanding of human biology as well as for food product development, economic progress, and future wealth creation. To date, however, much of the evidence is from animal, retrospective studies and short-term nutritional intervention studies in humans. The positive effect of micronutrients on health, especially of pregnant women eating well to maximise their child's cognitive and behavioural outcomes, is commonly acknowledged. The current evidence of an association between gestational nutrition and brain development in healthy children is more credible for folate, n-3 fatty acids, and iron. Recent findings highlight the fact that single-nutrient supplementation is less adequate than supplementation with more complex formulae. However, the optimal content of micronutrient supplementation and whether there is a long-term impact on child's neurodevelopment needs to be investigated further. Moreover, it is also evident that future studies should take into account genetic heterogeneity when evaluating nutritional effects and also nutritional recommendations. The objective of the present review is to provide a background and update on the current knowledge linking nutrition to cognition and behaviour in children, and to show

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how the large collaborative European Project NUTRIMENTHE is working towards this aim.

Keywords Nutrition · Children · Mental performance · Cognition · Brain assessment · Genetics

Abbreviations

AA	Arachidonic acid
ADHD	Attention-deficit hyperactivity disorder
ALA	Alpha-linolenic acid
aMRI	Anatomical magnetic resonance imaging
COMT	Catechol-*O*-methyltransferase
DHA	Docosahexaenoic acid
DNA	Deoxyribonucleic acid
EEG	Electroencephalogram
ELOVL	Fatty acid elongase 5
ERG	Electroretinogram
ERPs	Event-related potentials
FADS	Fatty acid desaturase
FFQ	Food frequency questionnaire
fMRI	Functional magnetic resonance imaging
GWA	Genome-wide association studies
HOTV	Single letters that are presented to the child using the Electronic Visual Acuity System
IQ	Intelligence quotient
LA	Linoleic acid
LC-PUFA	Long-chain polyunsaturated fatty acid
MRI	Magnetic resonance imaging
mRNA	Messenger ribonucleic acid
MTHFR	Methylenetetrahydrofolate reductase
NUTRIMENTHE	The Effect of Diet on the Mental Performance of Children
PET	Positron emission tomography
PUFA	Polyunsaturated fatty acid
RNA	Ribonucleic acid
T3	Triiodothyronine
T4	Thyroxine

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Introduction

Cognitive performance and the increase in mental health problems in children are of growing concern around the world. In Europe, atypical cognitive development and mental disorders, including anxiety, mood, and impulse-control disorders, are estimated to affect around 35 % of children, reducing their quality of life and leading to a significant cost impact on society. Mental disorders account for 8.1 % of the global burden of disease [1], and therefore, there is an increased need for research into their causes and consequences, and for the translation of this knowledge to policies and preventive programmes [1].

Studies carried out in humans and experimental animals demonstrate the crucial role of nutrition in neurodevelopment. Providing better nutrition has the potential to be a cost-effective approach in the prevention and management of mental health problems, especially in relation to nutrients such as essential fatty acids, iron, and zinc [1–3].

There is growing evidence that early nutrition can influence later cognitive development and behaviour in healthy children [4–6]. The idea that the diet of pregnant women, infants, and children could have a long-term influence on cognitive abilities has major implications for public health practice and policy development.

NUTRIMENTHE is a large European research collaboration studying the effects of early nutrition on later outcomes related to cognitive development (www.nutrimenthe.eu). NUTRIMENTHE aims to provide new knowledge on the cognitive performance of children through studying the role, mechanisms, risks, and benefits of specific nutrients and food components in neurodevelopment [7]. Due to the involvement of several large cohort studies and the inclusion of targeted interventions, important information will be generated, including quantification of early nutrient effects on later cognitive and behavioural development, such as attention, motivation, perception, memory, and mood.

The aim of the present review is to provide the background and current knowledge linking nutrition to cognition and behaviour in children, and to show the contribution to current knowledge of the large collaborative European Project NUTRIMENTHE. It will highlight where future work, to be carried out by NUTRIMENTHE, will aim to fill the gaps identified in this review.

Nutrition and neurodevelopment

Nutrition plays an important role in supporting structural and functional development of the human brain from conception through childhood and adolescence and into adulthood [8]. Brain development begins in the embryo and

continues into post-natal life. During the phase of rapid growth in the last trimester of gestation and the first 2 years after birth, the brain is particularly vulnerable to an inadequate diet [9, 10]. During the first 4 years of life, the brain reaches a weight of 1,200 g, which is only approximately 200 g less than that of an adult's brain. For the next 10–15 years, growth continues, but it is not uniform across the brain. For example, the thickness of the different regions of the cerebral cortex changes between the ages of 5 and 18 years at different rates; cortical regions important for reasoning, planning, and social communication appear to mature last. Nutrients might serve as critical signals, acting directly or via coupling mechanisms on 'receptors' in sensitive tissues [11]. Early events might have immediate effects on structural and functional development of the brain, and some nutrients are more likely to influence brain development than others. As a result, the brain is particularly sensitive to misprogramming due to its long period of development and specialisation. The consequences of *early misprogramming* of the brain will affect not only its structure and function, but will also impact on other body functions. For example, the brain is involved in the control of endocrine and inflammatory signalling from different '*brain–body axis*', regulating all metabolic processes involved in growth and development. The implications of the lack of certain nutrient(s) will depend on the stage of development at which the deficiency occurs, the degree of deficiency, and the duration of reduced supply.

Prenatal nutrition and neurodevelopment

The prenatal period is divided into three stages: the conceptual or germinal period, the embryonic period, and the foetal period [12]. Brain development begins 18 days after fertilisation, and it is one of the slowest organs to develop, continuing that process for many years after birth. Postnatal health may be influenced by prenatal factors, in line with the developmental origins of adult health hypothesis [13, 14], which states that the environment experienced during the individual's pre- and post-natal life 'programmes' the functional capacity of the individual's organs, with a subsequent effect on the individual's health. In order to establish the potential effects of nutrition, the development occurring at a particular time point in different areas of the brain must be taken into account [15].

It is well known that nutrients are vital to brain development, not only for morphological development, but also for brain neurochemistry and neurophysiology. During late foetal and early neonatal life periods, regions such as the hippocampus, the visual and auditory cortices, and the striatum undergo rapid development characterised by the morphogenesis and synaptogenesis that make them functional [16, 17].

When considering cognitive development, there are sensitive and critical stages of development during which environmental conditions, such as diet, can have a long-lasting influence. For any given region, *early malnutrition* has an effect on cell proliferation, thereby affecting cell number [16, 17]. For example, neonatal malnutrition can affect the volume and width of the cerebral cortex [18]. Neurochemical alterations include changes in neurotransmitter synthesis, receptor synthesis, and neurotransmitter reuptake mechanisms [19, 20]. Neurophysiologic changes reflect changes in metabolism and signal propagation. For instance, a dietary deficiency at a critical stage of development can result in permanent changes in brain structure and, therefore, cognitive functioning [21]. This means that both the diet of the mother during pregnancy and the diet of the infant in the perinatal period can have long-term consequences [22]. As the brain develops rapidly during pregnancy, poor nutritional intake can hinder the proper development of important brain structures [11]. Findings from the Dutch famine studies, for example, have shown that famine exposure during gestation had lasting negative consequences for the offspring's mental health [4, 23]. In animal studies, prenatal exposure to protein-calorie malnutrition is associated with neurotransmitter, cellular, electrophysiological, and behavioural disruptions similar to those found in patients with schizophrenia [24, 25].

Copper is an essential divalent cation for proteins involved in brain energy metabolism, dopamine metabolism, antioxidant activity, and iron accretion in the foetal and neonatal brain [26]. Micronutrients play a determinant role in the development of brain substrates for cognition. A deficiency of various micronutrients can have long-term implications for cognitive development in humans [9]. Vitamin A plays a key role in visual perception, and its deficiency is the leading cause of childhood blindness. It is also of particular importance during periods of rapid growth, both during pregnancy and in early childhood [9, 27]. Retinoic acid, a vitamin A derivate, has been shown to affect different molecular signalling pathways in the developing brain by regulating expression of several genes and promoting cell differentiation, making it important for the regulation of neurodevelopment [28]. Retinoic acid signalling has also been shown to be important for development for striatal functional pathways, which are involved in dopamine-regulated cognitive and motor activity [29]. In a recent study, thiamine deficiency during the first year of life was found to affect children's abilities selectively, yielding specific impairments in the language domains of syntax and lexical retrieval, but without affecting conceptual or general cognitive deficits [30].

The role of folate in early pregnancy in the prevention of neural tube defects is well established, and it is also fundamental for brain development due to its participation in

nucleotide synthesis, methylation processes, DNA integrity, and transcription [31]. Folates seem to have an effect on memory [32] and in conditions such as schizophrenia [33] and depression [34]. Systematic reviews and meta-analysis have shown that supplementation during pregnancy with a multivitamin containing folic acid does not result in a benefit to mental performance in children [35]. However, NUTRIMENTHE researchers have shown that low maternal folate status during early pregnancy is associated with increased risk of internalising (mood instability, obsessions, somatic problems, nervousness, insecurity, fears, phobias, sadness, apathy, dysphoria, restlessness, tension, worry, and guilt) and externalising (disruptive behaviours, irritability, impulsiveness, aggressiveness, and inattention) problems in young children [36, 37]. Cohort studies have shown that folate-supplemented mothers have children with fewer behavioural problems at 18 months of age [36], improved scores on verbal, verbal-executive functions, social competence, and attention measures at 4 years [38], and reduced hyperactivity and peer problems at 8 years [39].

Choline is required for the formation of all membranes, including grey and white matter phospholipids, with higher demands during growth [40–42]. Moreover, it influences DNA methylation, as it is a major dietary methyl donor (via betaine), thus having role in epigenetic mechanisms. Choline, folate, and homocysteine metabolism is closely interrelated, and the pathways for the metabolism of these nutrients intersect at the formation of methionine from homocysteine [41]. The developing central nervous system is particularly sensitive to choline availability with evidence that low choline availability leads to poor brain development and long-term cognitive and behavioural impairments in rodents [40, 41]. In pregnant women consuming a diet deficient in choline, increased incidence of neural tube defects and orofacial cleft defects in infants has been reported [40, 41]. Studies on adults have reported better cognitive function in those eating diets higher in choline [43], but adequately powered studies to determine whether choline nutrition during pregnancy enhances brain development, especially memory, in infants are lacking [42].

A lack of iodine and/or thyroid hormone, at the end of the first trimester and the early part of the second trimester of gestation, is associated with reduced intellectual ability and will result in irreversible abnormalities in brain development [44, 45]. Van Mil et al. [46] as part of NUTRIMENTHE (Generation R study), have shown that low maternal urinary iodine during early pregnancy is associated with impaired executive functioning of the child [14, 46]. Also in NUTRIMENTHE, Bath et al. [47] (ALSPAC study) showed that inadequate iodine status during early pregnancy is adversely associated with child cognitive development at 8 years. Further studies are needed, however, to demonstrate whether these children are more vulnerable to developing later clinical disorders or sustained cognitive impairment.

Zinc is also important as it plays a central role in the growth of cells. It can be found at high levels in the brain where it has both structural and functional tasks and it is essential both before and after birth for normal cognitive development [48, 49].

Iron deficiency during early life can also have an adverse effect on brain development. Very low prenatal levels of iron can induce changes in the myelination of neurons and in dopamine metabolism, which can persist if there is a deficiency of iron during the neonatal period [9, 50]. A recent systematic review of studies examining the influence of prenatal iron supplementation of pregnant women showed modest effects on psychomotor development of their children but no effect on their mental development or behaviour [51]. However, other studies have shown that perinatal iron deficiency produced an altered neurochemical profile of the developing hippocampus in children [52]. Another recent systematic review about iron supplementation in infants, children, and adolescents did not show any effects on either the IQ or behavioural status of their children; a higher incidence of children with teacher-rated peer problems at school was observed [53].

The n-3 fatty acid docosahexaenoic acid (DHA) and the n-6 fatty acid arachidonic acid (AA) are the major long-chain polyunsaturated fatty acids (LC-PUFAs). Brain accumulation of DHA starts in utero, with quantitatively marked deposition in the second half of gestation [54, 55] coinciding with the growth spurt in the grey matter. LC-PUFA supply to the foetus by the mother is mediated by maternal–foetal placental transfer during pregnancy, and breast milk provides fatty acids to infants after birth [56]. Higher maternal intake of DHA results in higher maternal plasma levels and thereby increased DHA transfer to the foetus [57]. Reduced DHA has been associated with dysfunctions in cognitive and behavioural performance in newborns [58]. Studies analysing the effect of prenatal LC-PUFA status or prenatal LC-PUFA supplementation indicate that an enhanced prenatal AA and DHA status might be related to improved neurodevelopmental outcomes until at least 18 months of age [59] and that later psychomotor development [60] and cognitive function in children may also benefit [61]. Hermoso et al. also concluded that maternal intake of very-long-chain n-3 PUFAs during pregnancy and lactation may be favourable for later mental development of children [62]. Nevertheless, recent reviews and meta-analysis of randomised clinical trials (RCTs) conclude that there is no clear long-term benefit of LC-PUFA supplementation during pregnancy

and/or lactation on child's neurodevelopment [63–65]. More adequately, powered studies of high methodological quality are clearly needed in this area, including large well-designed studies in humans, investigating the effects of early nutrition (including maternal supplementation during pregnancy) on child's neurodevelopment and health. The NUHEAL study [57] of the NUTRIMENTHE project is analysing long-term effects of LC-PUFAs and/or 5-MTHF supplementation on cognitive and behavioural outcomes in children up to the age of 9.5 years. This is a unique approach as the children have been assessed using the same battery of neuropsychological tests and have been followed up until the age of 9.5 years, which will hopefully clarify some aspects of the long-term effects of maternal fatty acid and/or folate supplementation on mental development in childhood. Furthermore, neurodevelopment outcomes of more than 1,000 children from eight different European countries have been examined within the NUTRIMENTHE project, using a neuropsychological battery specifically designed and translated into eight European languages for this purpose.

Infant and childhood nutrition and brain development and behaviour

Nutrition is one of many factors that affect brain development. As the brain continues to develop during childhood and adolescence, diet is likely to have an impact on cognitive ability and behaviour [44]. Meeting the nutritional demands for certain micronutrients is likely to have beneficial effects on cognitive development in school children [66–68]. Moreover, most evidence reported for iron, iodine, vitamin A, and zinc supplementation indicates that combined supplementation may have a greater effect on certain outcomes than supplementation with a single micronutrient [69].

Iodine deficiency can affect cognitive performance and development due to the broad impact of hypothyroidism on neuronal structure and function. Cross-sectional studies have shown that iodine deficiency has a negative effect on the cognitive performance of children, which was subsequently improved by iodine supplementation [70]. Randomised intervention studies with iodine in school-aged children have found evidence for enhanced cognitive performance, but these improvements were probably limited to those children showing previous iodine deficiency [44].

Increasing evidence seems to indicate that low iron status adversely influences psychological functioning as a consequence of decreased activity of iron-containing enzymes in the brain, in addition to reduced haemoglobin synthesis [9]. Many studies have been carried out on how iron deficiency affects children [50, 67, 71]. It appears that the timing of iron deficiency is of crucial importance; if it occurs during the first 6 or 12 months of life, the adverse effects on cognitive performance are likely to persist, even if iron intake subsequently achieves the recommended levels [72, 73]. It has been reported that iron deficiency during early infancy can affect the development of auditory processing and executive control and contribute to a higher incidence of behavioural problems and poor scholastic achievements [72]. Also, a systematic review and meta-analysis conducted by Falkingham et al. [74] have found some evidence that iron supplementation can improve attention and concentration in adolescents of baseline level of iron status. Nonetheless, further studies are needed as suggested by a recent systematic review of randomised controlled trials. This review, carried out by the NUTRIMENTHE team, concluded that the limited evidence available suggests that iron supplementation in infants may influence positively children's psychomotor development (Psychomotor Development Index), whereas it does not seem to alter their development or behaviour [51]. Similar conclusions were drawn in a systematic review recently performed as part of the EU-funded EURRECA project [53].

Zinc deficiency in children has been associated with reduced cognitive and motor performance [44], and with higher incidence of depression and ADHD [75]. Even though the exact mechanisms are not clear, it seems that zinc is essential for neurogenesis, neuronal migration, and synaptogenesis, and its deficiency could interfere with neurotransmission and subsequent behaviour [76].

The association between B vitamins, especially folate, and cognitive performance has also been investigated [77]. A recent study demonstrated a positive association between folate intake and academic achievements in 15-year-old school children, independent of socio-economic status and income of parents [78]. Vitamin B12 deficiency has also been shown to affect school performance of children aged 9–11 years [79]. The role of B vitamins on neural function in preschool children is being assessed in a double-blind randomised clinical trial as part of NUTRIMENTHE, the SIMBA trial (NCT00811291).

Protein deprivation can cause direct deleterious effects on the brain, such as reduced brain weight, altered hippocampal formation, impairment of neurotransmitter systems, and changes in protein phosphorylation [80]. Undernourished children (under 3 years of age) usually have delayed development, impaired behaviour, and lower school achievement, and supplementation studies have shown benefits on their development [81]. Currently, the effect of different protein intakes during the first 12 months of life on cognitive development and behaviour in boys and girls at 8.5 years is being analysed in NUTRIMENTHE (CHOP study) [82].

Choline has been shown to be an important nutrient during the early-post-natal period because, via epigenetic mechanisms, it has been shown to play an important role in the development and health outcomes later in life [41]. Mature human milk contains large amounts of choline, and the differences in choline composition (and bioavailability) between human milk and formulas appear to unfavourably affect the choline status in neonates [83]. Studies on rodents demonstrate that increased choline exposure during the prenatal period beneficially affects cognitive function [40]. Whether these findings are applicable to humans has yet to be investigated.

In relation to fatty acids, both omega-3 and omega-6 polyunsaturated fatty acids (PUFAs) have been associated with many health benefits and may also be relevant for the development of attention and problem-solving abilities [84]. Furthermore, fatty acid metabolism may be implicated in a cluster of neurodevelopmental disorders, including ADHD, dyslexia, dyspraxia, and the autistic spectrum [85]. It has been reported repeatedly that breastfed children attain higher intelligence quotient (IQ) scores than non-breastfed children. The fatty acids provided in breast milk are thought to play a crucial role in this respect [86]. In the ALSPAC study, researchers have observed that high maternal seafood consumption (more than 340 g per week) in pregnancy had beneficial effects on child development [87]. Breastfeeding is associated with advantages for child cognition [88–90] and infant temperament [91]. Kafouri et al. [92] have shown that the duration of breastfeeding is associated with cortical thickness, as assessed with magnetic resonance imaging in typically developing adolescents. A recent review indicated that neurodevelopment and cognitive abilities can be enhanced by early provision of n-3 LC-PUFAs through breast milk or DHA-fortified foods [64]. It is possible, however, that there is an optimum level of DHA below and above which DHA might be detrimental to the developing brain, and therefore, this suggests that further evidence is needed on long-term beneficial or harmful effect of LC-PUFA supplementation on neurodevelopment in term infants [64]. With respect to visual development, the European Food Safety Authority has confirmed that there is conclusive evidence for a causal relationship between the provision of DHA (in a proportion of at least 0.3 % of dietary fat in infancy) and improved visual function at the age of 1 year [93]. Nevertheless, recent reviews conclude that despite the numerous well-designed studies, there is still no clear and consistent benefit of LC-PUFA supplementation on child's neurodevelopment [64, 94]. Within NUTRIMENTHE project, a multicentric double-blind, randomised clinical trial of phenylketonuric patients (ageing 7–12 years) is ongoing. As these patients have a protein-restricted diet (but still accomplishing the minimal recommended protein intakes without eating fish), this is an excellent model for studying the influence of n-3 LC-PUFA intake on the cognitive and mental performance in childhood and to establish the quantitative requirements for children within the general population.

Methodological approaches to assess cognitive development, nutritional status, body composition, and physical activity

Neuropsychological development assessment

Cognitive function is a term used to describe several processes and functions, including the domains of language, memory, motor, perception, attention, and executive functions [95]. These abilities are not easy to measure even when using validated tests. For example, memory is a very complex set of processes (e.g. short-term, long-term, visual, spatial, verbal, declarative, semantic, and strategic), and each domain needs to be investigated using different assessment tools [96]. In the past, the most common cognitive outcome measure in nutrition studies has been intelligence quotient (IQ).

There have been many studies investigating the effect of nutritional intervention on cognitive performance in children. However, most have methodological problems [97, 98]. The first concern is related to the sensitivity of the neuropsychological tests to measure changes in cognitive performance, which might be related to nutritional change. This is because neuropsychological development is a heterogeneous process in which there are several critical periods involved [98]. The first brain regions to mature are those involved in visuo-motor balance and motor performance. Later, the regions involved in learning, memory, and language mature. Finally, it appears that cortical regions involved in cognitive control (prefrontal cortex) and social cognition (lateral temporal cortex) reach full maturity last. The effects of nutrition on cognitive performance may depend on the maturation stage at which the nutritional change happens, although one cannot rule out the possibility of delayed effects of early nutrition on the structure or function of the brain, only after it has reached full maturity. In addition, the neuropsychological tests need to assess specific neuropsychological domains (perceptual, motor, attention, learning and memory, and executive functions) instead of global cognitive performance, in order to detect which domain is affected [84, 99].

Another factor to be considered is the practice/learning effect [99]. When a neuropsychological procedure is going to be applied more than once, control of practice/learning effects is essential, especially if the intention is to test some improvement after a nutritional intervention [100]. All of

these suggest that any one test is not enough to detect significant changes in brain development because of a specific nutrient supplementation. Therefore, each study should have carefully designed, specific neuropsychological tools combining different neuropsychological domains to evaluate the potential effect of a nutrient, always taking into account the biological mechanism involved in the specific nutrient effect that is explored. In fact, the best approach seems to be the use of a battery of neuropsychological tests to assess a variety of cognitive domains at the same time [15].

The NUTRIMENTHE project has designed a harmonised neuropsychological protocol available in different languages, taking into account cultural differences between the different participating countries (see Table 1). This cross-cultural neuropsychological battery for cognitive assessment in EU children has been specifically designed to measure long-term effects of nutrition on cognitive development during childhood. This battery is currently being used in the studies of NUTRIMENTHE that have collected new data and is an important tool to provide comparable methodology for cognitive assessment in European children.

Table 1 NUTRIMENTHE neuropsychological battery

Domain	Function	Tests
Perception	Visuo-perceptual integration	HVOT
Motor	Visuo-motor coordination	Grooved pegboard test (GPT)
Attention	Spatial	Cancellation test (Woodcook-Muñoz)
	Sustained and focused	CPT
Memory	Visual episodic memory	Recall of objects test (British ability scale)
	Auditory memory	Auditory memory of Rey
Language	Semantic fluency	Animal-FAS
	Verbal comprehension	NEPSY's token test
Executive function	Update	Reversal digits (W-M)
		Matrix analogies (K-ABC II)
		Comprehensive trail making test (CTMT)
	Impulsivity/ inhibition	Go/no-go
		Stroop (five digit test) (1–3rd condition)
	Decision-making	Hungry donkey test (HDT)
Processing speed		Symbol digit modality test

Imaging techniques

A deficiency in one or more nutrients in the diet can disrupt the biochemical and morphological organisation of the brain, which is usually followed by repercussions on its function. Neurobehavioural assessments can be performed giving researchers an insight into brain structure and function [26]. It has been suggested that recent advances in neuroimaging methods have provided new ways of solving the complex interplay between genetic and environmental factors that influence brain development during the critical first years of life [101].

A number of techniques are available for the assessment of nutrition-related variations in brain structure and function (see Table 2). With the exception of positron emission tomography (PET), it is possible to apply all of the methods mentioned from childhood onward. For example, overall and regional brain volumes, as well as cortical thickness and white matter microstructure, can be measured by anatomical magnetic resonance imaging (MRI) scans; objective metrics of brain electrical function can be obtained by electroencephalogram (EEG), or evoked potentials (EP) and event-related potentials (ERPs) [102].

Table 2 Methodologies to explore brain development

Neuropsychological tests' study of different domains to assess:
Intelligence and mental performance
Psychomotor development
Behaviour maturation
Electrophysiological recording visual and auditory acuity
Sweep VEP
Transient flash VEP
Pattern-reversal stimuli VEP
Steady-state VEP
HVOT visual acuity
Sonksen–Silver acuity system
Teller acuity cards
Scotopic ERG
EEG
EEG/ERP
Neuroimaging brain structure and function
aMRI
fMRI
MEG
PET

aMRI = anatomical magnetic resonance imaging, EEG = electroencephalography, ERG = electroretinogram, ERP = event-related potentials, fMRI = functional magnetic resonance imaging, HVOT = single letters that are presented to the child using the Electronic Visual Acuity System [175–177], MEG = magnetoencephalography, PET = positron emission tomography, VEP = visual evoked potential

An EP or ERP is any stereotyped electrophysiological response to an internal or external stimulus. ERPs can be reliably measured using EEG, a method that measures electrical activity of the brain (the synchronised electrical signal from a large number of neurons) through the skull and scalp. Measuring differences in EEG, averaged across many trials, allows researchers to study changes in brain activity in response to stimuli [103].

Another available technology in neuroscience is functional magnetic resonance imaging (fMRI), a technique for measuring brain activity. It works by detecting the change in blood oxygenation levels that occur during neural activity. Detailed three-dimensional 'pictures' of the brain are created, each consisting of thousands of three-dimensional image elements named voxels [8]. Functional MRI can be used to produce activation maps showing which parts of the brain are involved in a particular cognitive process.

In summary, the timing of a number of cognitive processes can be obtained using electrophysiological measurements, whereas functional magnetic resonance imaging provides insight into the location of regions associated with a specific cognitive task [8]. All these non-invasive methods for measuring brain activity during cognitive processing hold promise for identifying the neural subprocesses involved in complex cognitive, motor, or perceptual tasks. They can be time-linked to the stimulus onset (e.g. the presentation of a word, a sound, or an image) and have been used in infants and children with some success [104]. A number of MRI studies have been designed and conducted in typically developing children and adolescents [105]. MRI is also being used in Generation R, a prospective cohort study from foetal life until young adulthood in a multi-ethnic urban population in the Netherlands [106], which is also taking part in the NUTRIMENTHE project. The study was designed to identify early environmental and genetic causes of normal and abnormal growth, development, and health from foetal life until young adulthood. In total, 9,778 mothers were enrolled in the study and extensive data have been collected during pregnancy, and the children are being followed at set ages after birth. Researchers of this study are now working to obtain advanced brain (including structural and functional MRI) data in all children of 6 years of age and older. This will generate an important and unique contribution to the already impressive Generation R project.

The EEG/ERP technique is also being used in NUTRIMENTHE as part of the NUHEAL study in three different countries. Preliminary results indicate that children born to mothers supplemented with 5-MTHF, when presented with the working memory (WM) task, were able to solve it more quickly and appeared to need fewer control resources in general, and specifically less involvement of the key nodes of an 'executive network', such as the dorsolateral prefrontal cortex, to solve the task, compared to children not exposed to added folate. In conclusion, children born to mothers supplemented with 5-MTHF during pregnancy performed the WM task more quickly, with less involvement of the control areas of the brain, than those whose mothers did not receive 5-MTHF during pregnancy.

Dietary intakes and eating behaviours

There are several methods that can be used to assess dietary intake in groups of individuals, and in NUTRIMENTHE two different methods have been used to maximise the range of data collected. Food frequency questionnaires (FFQs) designed to assess habitual diet by asking about the frequency with which food items or specific food groups are consumed over a reference period (e.g. 6 months or a year) have been used [107, 108]. These have been particularly important in assessing the diet of the women in pregnancy and have been used by NUTRIMENTHE partners to show that the eating of fish by the mother in pregnancy is associated with better visual and cognitive outcomes in their children [87, 109]. The use of FFQs has some advantages; since responses are standardised, dietary data on a large number of people can be collected and analysed economically. FFQs can be used to identify patterns of food intake using statistical methods such as principal component analysis [110] and cluster analysis [111], and these may be associated with inadequate intakes of specific nutrients and with the outcomes being studied. When using FFQs to assess diet, however, there is a lack of detail about the food consumed because subjects can only answer the questions as given and they may not fit well with the diet actually eaten and there is no assessment of how and when food is eaten. For FFQs to work well, they need to be designed specifically for, and tested in, the population and age group being assessed and, if being used across countries, need to be carefully adapted to the food habits of each country. These aspects need input from experienced nutritionists in each country, and this can often be neglected leading to unsatisfactory assessment of diet.

The second method used when assessing the diets of NUTRIMENTHE children is the collection of diet diary records of food and drink at the time of consumption. Parents are provided with a structured diary and an explanation, either on paper or in person, of how to complete the record. Typically, they complete the food diary (for 3 or more days) on behalf of the child and bring it with them to a clinic where the child is weighed and measured, and a short interview with a nutritionist is used to obtain extra information about the foods. This allows maximum flexibility in the description of food eaten, provides meal timings and information about food left over by the child. Turning this information into meaningful computerised

data is, however, time-consuming and requires trained staff with an understanding of nutrition and the local diet. If a reasonable number of individuals (50 or more) are assessed, the data collected by this method can be extremely valuable because they can be analysed in a variety of ways that do not necessarily need to be prespecified, so that research questions that arise during a project can be followed up relatively easily.

In NUTRIMENTHE a dynamic diet working group has been set up, where nutritional expertise is shared between studies, maximising the effectiveness of the dietary data collections in the different studies. The diet working group has investigated ways of improving comparability between diets eaten in different countries, where food habits are different, and the use of a common categorisation of food groups for the analysis is planned. Having harmonised the way in which food groups are defined, their contribution to the diet and their relationship with mental development and performance will be assessed. Furthermore, the food groups will be used in dietary pattern analysis (see above), and their relationship with the outcomes will be assessed. The use of food groups in this way will mean that the fact that different nutrient databases have been used in different countries is much less important and, because the public understands health messages about food more easily than messages about nutrients, it will facilitate the communication of any findings.

Assessment of anthropometry and body composition

Body size and composition are clearly affected by nutrition, and in turn, body characteristics may affect cognition and mental health. Head circumference has been related to the size of the brain [112]. In preterm and low-birthweight infants, head circumference has been associated with cognitive performance [112–115]. The first year of life is the period when the brain and the head grow the most [116, 117]. Therefore, this might be the period during which head measurement could be an indicator for later cognitive performance. There are no large multicentre studies studying the relationship between head circumference, growth velocity during the first months of life, and later cognitive performance. NUTRIMENTHE aims to fill that gap.

Other aspects of child's body size and composition could be related to cognition and mental health. One of the most important might be overweight and obesity. Obesity could influence psychosocial problems such as poor self-esteem, depression, and eating disorders [118–120]. A recent review examining 12 studies that explored the connection between maternal obesity and cognitive, behavioural, and emotional problems in the offspring concluded that the offspring of obese women may be at increased risk of behavioural and cognitive deficits in childhood, as well as eating disorders in adolescence and psychotic disorders in adulthood [121]. Childhood overweight and obesity could be related to cognitive performance as it has been shown to be related to executive functions. In children, there is preliminary evidence of a relationship between obesity and deficits in attention and shifting (the ability that the child has to redirect the focus of attention) [122] and deficits in the inhibitory control component [123]. Overweight adolescents have also shown emotion-driven impulsivity and cognitive inflexibility [124, 125]. It is possible that an impulsive child may not inhibit their intake of food, which may lead to weight gain and psychosocial problems.

The NUTRIMENTHE project aims to relate the different aspects of body size and composition with cognition and mental health, taking into account other possible factors such as socio-economic status, physical activity and/or inactivity, and maternal mental health. To achieve this goal in the NUTRIMENTHE cohorts, children have been measured from birth at various ages, following standard operating procedures (WHO recommendations, based in Lohman standards) [126, 127]. This longitudinal, multicentre approach will provide important evidence about the relationship between body characteristics and mental performance.

Assessment of physical activity

Physical activity is a factor that influences nutritional status and brain function. Human and animal studies have shown that aerobic exercise can improve different aspects of cognition, brain function, and mental health both in children and in adults [128–130]. Thus, accurate measurement of physical activity is a prerequisite for monitoring population health and for evaluating effective interventions [131]. There are various methods for measuring physical activity in large-scale epidemiological studies. These methods can be classified as objective methods (using monitors) and self-report methods (using questionnaires or interviews). The first can provide reasonably accurate quantitative measures of physical activity, and the second can be used to obtain qualitative data and to rank individuals into different levels of physical activity. To obtain the best-quality data, a combination of both types of method is recommended [132, 133]. Heart rate can also be monitored using a portable heart rate recorder, and together with the use of an activity diary in which the subjects record their activities, it is possible to get a relatively complete view of the physical activity carried out [134].

Accelerometry-based monitors are the most widely used objective techniques to assess physical activity in children [135]. Several accelerometers have been validated for use in children, although they still have some limitations [136].

In the NUTRIMENTHE project, the Armband Sense Wear (Bodymedia), a multisensor that combines accelerometry and heat-flux sensors, is being used to objectively monitor physical activity over a 24-h period. The data obtained can be used to estimate energy expenditure using validated algorithms for children [137]. The information recorded through the armband monitor is combined with information collected through validated physical activity questionnaires [138, 139] and records of screen activities (TV-viewing, computer, and video games). Within NUTRIMENTHE (NUHEAL and CHOP studies), all this valuable information is collected from the participating children in different European countries and will be used to assess the relationships between physical activity and cognitive behaviour and development. This project will significantly contribute to the existing literature by comprehensively exploring how children with different physical activity levels, objectively measured, differ in relevant cognitive and neurodevelopmental factors, as well as in brain structure and function. In addition, due to the longitudinal dimension of this project, we will be able to examine whether maternal lifestyle factors might have a programming effect on their offspring's physical activity levels.

Genetic factors influencing nutrition and neurodevelopment

Genetics

The human genome project has brought forth a wealth of information on the structure of the genome and increased our understanding of how the interplay between our genes and nutrition relates to a state of health or disease, i.e. nutrigenetics.

The tissue composition of PUFAs is important to child's neurodevelopment and depends on both dietary intake and metabolism, controlled by genetic polymorphisms as shown by recent studies. The delta-5 and delta-6 desaturase enzymes, encoded by the *FADS1* and *FADS2* genes, play important roles in PUFA metabolism and can influence PUFA and LC-PUFA tissue availability, as shown by NUTRIMENTHE collaborators [140–146]. *FADS* gene variants account up to 28.5 % of the variability in the PUFA and LC-PUFA levels in human tissues [147, 148]. Therefore, blood and tissue levels of the essential fatty acids LA and ALA and of their biologically active LC-PUFA derivatives are influenced not only by diet, but to a large extent also by genetic variation.

The first study demonstrating a favourable effect of a genetic variant on IQ in breastfed children was conducted by Caspi et al. [149], where a marked IQ advantage for breastfed children carrying the common *FADS2* rs174575 C allele was shown, over children not breastfed. In minor G allele carriers, breastfeeding had no influence on IQ [149]. A further study conducted by NUTRIMENTHE researchers also demonstrated that these two *FADS2* variants significantly altered the effect of post-natal breastfeeding on the intelligence quotient achieved at age 8, where children carrying rs174575 GG had the lowest average IQs amongst formula-fed children, but when breastfed, their scores were similar to CC and CG children [150]. Additionally, a recent study on *FADS* gene cluster and the *ELOVL* gene family (involved in the elongation of LC-PUFAs) concluded that genetically determined maternal supplies of LC-PUFAs during pregnancy and lactation influence infant brain development and that breastfeeding effects on cognition are modified by child genetic variation [88]. Also, an association between apolipoprotein E isoforms and neuronal/brain development in infants has been shown [151].

Another interesting pathway in nutrigenetics effects is the folate-mediated one-carbon metabolism, where two cycles are intertwining and competing for folate cofactors: DNA biosynthesis and methylation cycle [152]. Folate (vitamin B_9) participates in one-carbon biosynthetic and epigenetic processes that facilitate the synthesis and methylation of nucleic acids and proteins. Several variations have been identified in genes involved in the folate absorption and folate-mediated one-carbon metabolism [153], where *MTHFR* 677 C/T seems to be the most important in terms of prevalence and impact [154]. MTHFR enzyme regulates folate availability, and the 677 TT genotype is associated with 60 % reduced enzyme activity, which results in the accumulation of homocysteine and impaired methylation reactions [155]. The maternal *MTHFR* 677 T allele has been reported as an independent predictor of poorer child neurodevelopment at 24 months of age, whereas child's *MTHFR* 677 C/T genotypes did not associate with child neurodevelopment [156]. Also, polymorphisms in genes involved in choline production have an effect on one-carbon metabolism [41]. Common polymorphisms in *PEMT* gene promoter region (rs12325817), *MTHFD1* gene (1958 G/A), and *CHDH* gene (432 G/T) result in metabolic inefficiencies in choline metabolism; thus, more choline is needed as a methyl donor to replace missing methyltetrahydrofolate [41, 42].

These results refer to the effect of maternal–foetal metabolism of folate that maternal genetic variation in folate metabolism during pregnancy may programme offspring neurodevelopment trajectories [156].

In a recent study, maternal gene variants *MTHFR* 677 TT (rs1801133 C/T), *CBS* rs2234715 GT + TT, and *COMT* AA (rs4680 G/A) were associated with mental disorder and with greater autism risk in children in the absence of periconceptional prenatal vitamin supplementation, which is known to confer less efficient one-carbon metabolism and thus higher homocysteine levels [157].

In conclusion, in order to obtain adequate understanding of the effect of nutrition on childhood neurodevelopment, future research should take into account genetic variation. This is particularly important when studying the key enzymes of LC-PUFA synthesis and folate-mediated one-carbon metabolism, and NUTRIMENTHE focuses on interactions between nutrition and genetic variation in genes related to fatty acid and folate metabolism in mothers and children with respect to neurodevelopment of children.

Omics

Diet is one of the most important environmental factors interacting with the genome to modulate disease risk [158]. Nutrigenomics offers a powerful approach to unravel the effects of nutrition on health in different levels by employing high-throughput genomics technologies [159] (see Fig. 1). Genome-wide association studies (GWAs), gene and protein expression analyses (transcriptome and proteome, respectively), organisation and modification of the chromatin structure (epigenome), as well as metabolite patterns (metabolome) bear great potential to gain better insights into the complexity of biological systems [160].

Recent GWA studies provide further evidence for the importance of the *FADS* gene cluster variation in PUFA metabolism [148, 161, 162]. Nutrigenomics studies on the regulation of genome, proteome, and metabolome by nutrients in humans are still limited, partly because it is a relatively new field and partly because of the high cost of genomics technologies [160]. Nevertheless, the few studies on humans published so far clearly indicate that changes in dietary fatty acids intake and composition can have an effect on cellular adaptive response capacity by gene transcription changes [160].

With the growing use of novel techniques, the knowledge of nutrient–gene/genome interactions will increase substantially. It will be for future studies to confirm and identify new genetic players that influence nutrient status in the human body with a possible effect on mental development. A novel aspect of the NUTRIMENTHE project is the assessment of metabolomics from child's urine samples and from blood samples. Changes in the metabolome are the ultimate answer of an organism to genetic variation, disease, or environmental influences; the metabolome is, therefore, most predictive of phenotype. Within NUTRIMENTHE, the key metabolites, e.g. amino acids, hormones (e.g. insulin, leptin), and status markers (phospholipid fatty acids), are being measured in infants and children, which will provide a comprehensive picture of the influence of early diet on child's nutritional status, metabolism, and brain structure and function.

Epigenetics

Unlike genetic information, which is very stable, epigenetic events are reversible and respond to endogenous and exogenous (environmental) signals [163]. The term 'epigenetics' refers to chromatin modifications that result in altered gene expression without changes in the DNA sequence itself [164]. Several epigenetic mechanisms have been described, including short RNA molecules

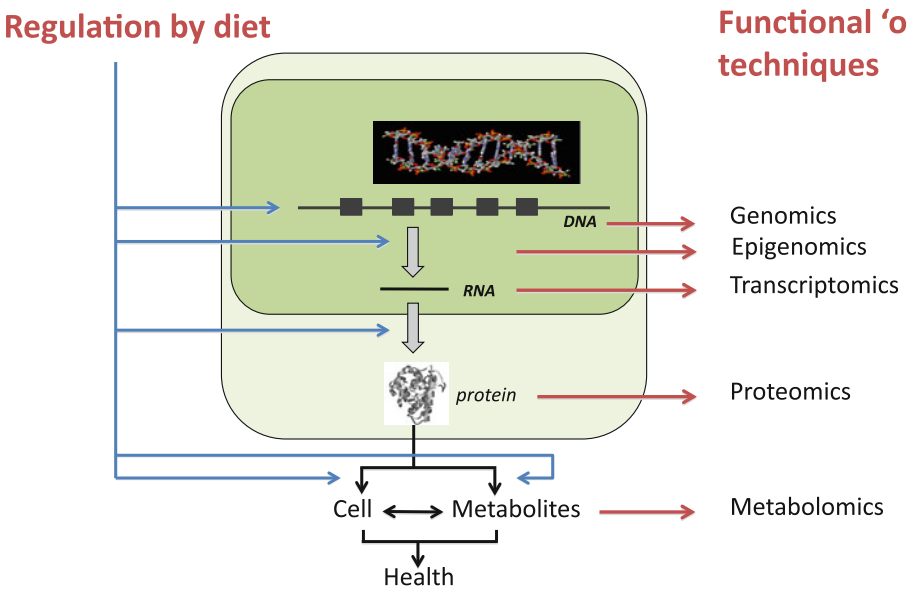

Fig. 1 Diet effects on cell. 'Omics' techniques for studying different levels such as genome, epigenome, transcriptome, proteome, and metabolome are indicated

(microRNAs), which bind to mRNA and thus modify gene expression [165], and DNA methylation and post-translational modifications of nucleosomal histones resulting in either up- or down-regulation of gene transcription [163]. Epigenetic markers serve as a memory of early-life exposure to inappropriate environments (nutritional, social) by long-term modifications of gene expression programming [166]. Research in developmental and behavioural neuroscience is providing growing evidence that the epigenome is exquisitely sensitive to environmental influences and thus influences cognitive health and risk for psychopathology throughout the lifespan [167].

Epigenetic 'misprogramming' during development is believed to have a persistent effect on offspring health and may even be transmitted to the next generation [168]. The Dutch Hunger Winter (1944–1945) [169] and the Chinese Famine (1959–1960) [170] demonstrate two extreme examples of how epigenetic effects triggered by extreme intrauterine nutritional deficiency may increase the risk of health problems in children, including impaired mental health. Dietary factors, including one-carbon metabolism pathway along with folate and other vitamins, play an important role in DNA synthesis and in the establishment of epigenetic modifications like DNA/histone methylation. In humans it has been demonstrated that periconceptional folic acid use is associated with epigenetic changes in the *IGF2* gene in the offspring that may affect intrauterine programming of growth and development with consequences for health and disease throughout life [171]. In addition, periconceptional undernutrition by caloric restriction has altered methylation patterns of a number of genes in later life [172].

Despite recent research, we are still far from understanding how, when, and where environmental factors interact with epigenetic mechanisms. Given the complexity of epigenetics, it remains a challenging issue for future studies to identify the role of various epigenetic participants in a given pathophysiological condition [168].

Conclusions and future challenges

It is accepted that maternal nutritional status in pregnancy can influence foetal brain development, which in turn affects behavioural and cognitive function in childhood. The evidence of an association between gestational nutrition and brain development seems to be more credible for folate, n-3 fatty acids, and iron [173]. Also, the positive effect of micronutrients on health, especially of pregnant women eating well to maximise their child's cognitive outcomes, is commonly acknowledged. Recent findings highlight the fact that single-nutrient supplementation is less adequate than supplementation with more complex formulae [173]. However, the optimal content of micronutrient supplementation, and whether there is a long-term impact on neurodevelopment in childhood, needs to be investigated further.

There is also growing evidence that an individual's genetic background (genetic variation) can influence nutrient status in the body [88, 144, 150, 174], which in turn can contribute to maternal-to-infant nutrient transfer and thereby influence the child's mental development. Thus, performing population-scaled epidemiological studies in the absence of genetic knowledge may result in erroneous scientific conclusion and misinformed nutritional recommendations. It is evident that future studies should take into account genetic heterogeneity when evaluating nutritional effects and also nutritional recommendations. In fact, it was recently proposed that periconceptional use of prenatal vitamins might reduce the risk of having children with autism, especially for genetically susceptible mothers and children [71, 157]. Novel studies are demonstrating that acquired epigenetic alterations can be inherited and can be pharmacologically reversed [167]. Understanding the role of the epigenome is not only relevant to help to understand how early-life experiences confer either risk or resilience regarding later mental development, but will be important and relevant to future therapeutics [167]. One of the key challenges for future studies will be to establish how, when, and where early nutrition influences children's mental health, both on epigenetic and on genetic level.

The NUTRIMENTHE project focuses on these questions by assessing the short- and long-term effects of pre- and early-post-natal diet on children's mental performance through well-designed large-scale epidemiological studies. Moreover, the optimal content and effect of specific nutrients initiated during pregnancy, infancy, and childhood are being analysed by follow-up of randomised clinical intervention trials. Additionally, the novel aspect of nutrigenetics (the interaction between nutrition and genetic variation with respect to childhood mental development) and metabolomics is being examined within NUTRIMENTHE. All these aspects have been discussed in this review, which also describes the methodological approaches being taken by NUTRIMENTHE, evaluating the weakness and positive outcomes obtained, in order to serve as a reference for future studies.

It is said that nutritional science is entering a new era with a shift away from 'little science' towards 'big science', defining the new era as 'Nutritional Science 2.0' [160]. These authors concluded that those major nutritional problems that have, currently, a huge impact on public health (e.g. obesity, diabetes, malnutrition) need multiple groups to work together in large national and international consortia to understand and solve the problems. NUTRIMENTHE is an intra-European consortium gathering top

researchers in the field of nutrition, paediatrics, psychology, psychiatry, and genetics in order to advance our knowledge of how nutrition affects mental health in childhood. The knowledge obtained by NUTRIMENTHE will contribute to the science base for dietary recommendations for pregnant women and children for improving mental health. The identification and application of nutritional recommendations is ultimately of broad social significance for the general population in terms of how it affects health behaviour, education, work potential, and mental illness in every age group.

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References

1. Ramakrishnan U, Imhoff-Kunsch B, DiGirolamo AM (2009) Role of docosahexaenoic acid in maternal and child mental health. Am J Clin Nutr 89:958S–962S
2. Bodnar LM, Wisner KL (2005) Nutrition and depression: implications for improving mental health among childbearing-aged women. Biol Psychiatry 58:679–685
3. McNamara RK, Carlson SE (2006) Role of omega-3 fatty acids in brain development and function: potential implications for the pathogenesis and prevention of psychopathology. Prostaglandins Leukot Essent Fatty Acids 75:329–349
4. Painter RC, Roseboom TJ, Bleker OP (2005) Prenatal exposure to the Dutch famine and disease in later life: an overview. Reprod Toxicol 20:345–352
5. Fleming TP, Kwong WY, Porter R, Ursell E, Fesenko I, Wilkins A, Miller DJ, Watkins AJ, Eckert JJ (2004) The embryo and its future. Biol Reprod 71:1046–1054
6. Koletzko B, Brands B, Demmelmair H (2011) The Early Nutrition Programming Project (EARNEST): 5 y of successful multidisciplinary collaborative research. Am J Clin Nutr 94:1749S–1753S
7. Horton C (2013) Network health dietitians. 84:28–29
8. Paus T (2010) A primer for brain imaging: a tool for evidence-based studies of nutrition? Nutr Rev 68(Suppl 1):S29–S37
9. Benton D (2008) Micronutrient status, cognition and behavioral problems in childhood. Eur J Nutr 47(Suppl 3):38–50
10. Dobbing J (1985) Infant nutrition and later achievement. Am J Clin Nutr 41:477–484
11. Benton D (2010) Neurodevelopment and neurodegeneration: are there critical stages for nutritional intervention? Nutr Rev 68(Suppl 1):S6–S10
12. Moore K and Persaud P (2003) The developing human: clinically oriented embryology, 7th edn. Lavoisier
13. Gluckman PD, Hanson MA, Pinal C (2005) The developmental origins of adult disease. Matern Child Nutr 1:130–141
14. Koletzko B, Brands B, Poston L, Godfrey K and Demmelmair H (2012) Early nutrition programming of long-term health. Proc Nutr Soc 1–8
15. Isaacs E, Oates J (2008) Nutrition and cognition: assessing cognitive abilities in children and young people. Eur J Nutr 47(Suppl 3):4–24
16. Nelson CA, Bloom FE, Cameron JL, Amaral D, Dahl RE, Pine D (2002) An integrative, multidisciplinary approach to the study of brain-behavior relations in the context of typical and atypical development. Dev Psychopathol 14:499–520
17. Thompson RA, Nelson CA (2001) Developmental science and the media. Early brain development. Am Psychol 56:5–15
18. Bedi KS, Bhide PG (1988) Effects of environmental diversity on brain morphology. Early Hum Dev 17:107–143
19. Beard JL, Connor JR (2003) Iron status and neural functioning. Annu Rev Nutr 23:41–58
20. Rao R, Tkac I, Townsend EL, Gruetter R, Georgieff MK (2003) Perinatal iron deficiency alters the neurochemical profile of the developing rat hippocampus. J Nutr 133:3215–3221
21. Benton D (2012) Vitamins and neural and cognitive developmental outcomes in children. Proc Nutr Soc 71:14–26
22. Benton D (2008) The influence of children's diet on their cognition and behavior. Eur J Nutr 47(Suppl 3):25–37
23. Roseboom T, de Rooij S, Painter R (2006) The Dutch famine and its long-term consequences for adult health. Early Hum Dev 82:485–491
24. Brown AS, Susser ES (2008) Prenatal nutritional deficiency and risk of adult schizophrenia. Schizophr Bull 34:1054–1063
25. Palmer AA, Printz DJ, Butler PD, Dulawa SC, Printz MP (2004) Prenatal protein deprivation in rats induces changes in prepulse inhibition and NMDA receptor binding. Brain Res 996:193–201
26. Georgieff MK (2007) Nutrition and the developing brain: nutrient priorities and measurement. Am J Clin Nutr 85:614S–620S
27. Sommer A (1982) Nutritional blindness, xerophthalmia and keratomalacia. Oxford University Press, New York
28. Luo T, Wagner E, Drager UC (2009) Integrating retinoic acid signaling with brain function. Dev Psychol 45:139–150
29. Liao WL, Tsai HC, Wang HF, Chang J, Lu KM, Wu HL, Lee YC, Tsai TF, Takahashi H, Wagner M, Ghyselinck NB, Chambon P, Liu FC (2008) Modular patterning of structure and function of the striatum by retinoid receptor signaling. Proc Natl Acad Sci USA 105:6765–6770
30. Fattal I, Friedmann N, Fattal-Valevski A (2011) The crucial role of thiamine in the development of syntax and lexical retrieval: a study of infantile thiamine deficiency. Brain 134:1720–1739
31. Reynolds E (2006) Vitamin B12, folic acid, and the nervous system. Lancet Neurol 5:949–960
32. Durga J, van Boxtel MP, Schouten EG, Kok FJ, Jolles J, Katan MB, Verhoef P (2007) Effect of 3-year folic acid supplementation on cognitive function in older adults in the FACIT trial: a randomised, double blind, controlled trial. Lancet 369:208–216

33. Garcia-Miss Mdel R, Perez-Mutul J, Lopez-Canul B, Solis-Rodriguez F, Puga-Machado L, Oxte-Cabrera A, Gurubel-Maldonado J and Arankowsky-Sandoval G. (2010) Folate, homocysteine, interleukin-6, and tumor necrosis factor alfa levels, but not the methylenetetrahydrofolate reductase C677T polymorphism, are risk factors for schizophrenia. J Psychiatr Res 44:441–446
34. Coppen A, Bolander-Gouaille C (2005) Treatment of depression: time to consider folic acid and vitamin B12. J Psychopharmacol 19:59–65
35. Skorka A, Gieruszczak-Bialek D, Piescik M, Szajewska H (2012) Effects of prenatal and/or postnatal (maternal and/or child) folic acid supplementation on the mental performance of children. Crit Rev Food Sci Nutr 52:959–964
36. Roza SJ, van Batenburg-Eddes T, Steegers EA, Jaddoe VW, Mackenbach JP, Hofman A, Verhulst FC, Tiemeier H (2010) Maternal folic acid supplement use in early pregnancy and child behavioural problems: the Generation R Study. Br J Nutr 103:445–452
37. Steenweg-de Graaff J, Roza SJ, P. SEA, Hofman A, Verhulst FC, Jaddoe VW and Tiemeier H (2012) Maternal folate status in early pregnancy and child emotional and behavioral problems. The Generation R Study. Am J Clin Nutr
38. Julvez J, Fortuny J, Mendez M, Torrent M, Ribas-Fito N, Sunyer J (2009) Maternal use of folic acid supplements during pregnancy and four-year-old neurodevelopment in a population-based birth cohort. Paediatr Perinat Epidemiol 23:199–206
39. Schlotz W, Jones A, Phillips DI, Gale CR, Robinson SM, Godfrey KM (2010) Lower maternal folate status in early pregnancy is associated with childhood hyperactivity and peer problems in offspring. J Child Psychol Psychiatry 51:594–602
40. Caudill MA (2010) Pre- and postnatal health: evidence of increased choline needs. J Am Diet Assoc 110:1198–1206
41. Corbin KD, Zeisel SH (2012) The nutrigenetics and nutrigenomics of the dietary requirement for choline. Prog Mol Biol Transl Sci 108:159–177
42. Zeisel SH (2013) Nutrition in pregnancy: the argument for including a source of choline. Int J Womens Health 5:193–199
43. Poly C, Massaro JM, Seshadri S, Wolf PA, Cho E, Krall E, Jacques PF, Au R (2011) The relation of dietary choline to cognitive performance and white-matter hyperintensity in the Framingham Offspring Cohort. Am J Clin Nutr 94:1584–1591
44. Bryan J, Osendarp S, Hughes D, Calvaresi E, Baghurst K, van Klinken JW (2004) Nutrients for cognitive development in school-aged children. Nutr Rev 62:295–306
45. Zimmermann M, Delange F (2004) Iodine supplementation of pregnant women in Europe: a review and recommendations. Eur J Clin Nutr 58:979–984
46. van Mil NH, Tiemeier H, Bongers-Schokking JJ, Ghassabian A, Hofman A, Hooijkaas H, Jaddoe VW, de Muinck Keizer-Schrama SM, Steegers EA, Visser TJ, Visser W, Ross HA, Verhulst FC, de Rijke YB, Steegers-Theunissen RP (2012) Low urinary iodine excretion during early pregnancy is associated with alterations in executive functioning in children. J Nutr 142(12):2167–2174. doi:10.3945/jn.112.161950
47. Bath SC, Steer CD, Golding J, Emmett P and Rayman MP (2013) Effect of inadequate iodine status in UK pregnant women on cognitive outcomes in their children: results from the Avon Longitudinal Study of Parents and Children (ALSPAC). Lancet
48. Black MM (1998) Zinc deficiency and child development. Am J Clin Nutr 68:464S–469S
49. Benton D (2010) The influence of dietary status on the cognitive performance of children. Mol Nutr Food Res 54:457–470
50. Lozoff B (2007) Iron deficiency and child development. Food Nutr Bull 28:S560–S571
51. Szajewska H, Ruszczynski M, Chmielewska A (2010) Effects of iron supplementation in nonanemic pregnant women, infants, and young children on the mental performance and psychomotor development of children: a systematic review of randomized controlled trials. Am J Clin Nutr 91:1684–1690
52. Georgieff MK (2008) The role of iron in neurodevelopment: fetal iron deficiency and the developing hippocampus. Biochem Soc Trans 36:1267–1271
53. Hermoso M, Vucic V, Vollhardt C, Arsic A, Roman-Vinas B, Iglesia-Altaba I, Gurinovic M, Koletzko B (2011) The effect of iron on cognitive development and function in infants, children and adolescents: a systematic review. Ann Nutr Metab 59:154–165
54. Clandinin MT, Chappell JE, Leong S, Heim T, Swyer PR, Chance GW (1980) Extrauterine fatty acid accretion in infant brain: implications for fatty acid requirements. Early Hum Dev 4:131–138
55. Martinez M (1992) Tissue levels of polyunsaturated fatty acids during early human development. J Pediatr 120:S129–S138
56. Koletzko B, Lien E, Agostoni C, Bohles H, Campoy C, Cetin I, Decsi T, Dudenhausen JW, Dupont C, Forsyth S, Hoesli I, Holzgreve W, Lapillonne A, Putet G, Secher NJ, Symonds M, Szajewska H, Willatts P, Uauy R (2008) The roles of long-chain polyunsaturated fatty acids in pregnancy, lactation and infancy: review of current knowledge and consensus recommendations. J Perinat Med 36:5–14
57. Krauss-Etschmann S, Shadid R, Campoy C, Hoster E, Demmelmair H, Jimenez M, Gil A, Rivero M, Veszpremi B, Decsi T, Koletzko BV (2007) Effects of fish-oil and folate supplementation of pregnant women on maternal and fetal plasma concentrations of docosahexaenoic acid and eicosapentaenoic acid: a European randomized multicenter trial. Am J Clin Nutr 85:1392–1400
58. Uauy R, Hoffman DR, Mena P, Llanos A, Birch EE (2003) Term infant studies of DHA and ARA supplementation on neurodevelopment: results of randomized controlled trials. J Pediatr 143:S17–S25
59. Hadders-Algra M, Bouwstra H, van Goor SA, Dijck-Brouwer DA, Muskiet FA (2007) Prenatal and early postnatal fatty acid status and neurodevelopmental outcome. J Perinat Med 35(Suppl 1):S28–S34
60. Escolano-Margarit MV, Ramos R, Beyer J, Csabi G, Parrilla-Roure M, Cruz F, Perez-Garcia M, Hadders-Algra M, Gil A, Decsi T, Koletzko BV, Campoy C (2011) Prenatal DHA status and neurological outcome in children at age 5.5 years are positively associated. J Nutr 141:1216–1223
61. Campoy C, Escolano-Margarit MV, Ramos R, Parrilla-Roure M, Csabi G, Beyer J, Ramirez-Tortosa MC, Molloy AM, Decsi T and Koletzko BV (2011) Effects of prenatal fish-oil and 5-methyltetrahydrofolate supplementation on cognitive development of children at 6.5 y of age. Am J Clin Nutr 94:1880S–1888S
62. Hermoso M, Vollhardt C, Bergmann K, Koletzko B (2011) Critical micronutrients in pregnancy, lactation, and infancy: considerations on vitamin D, folic acid, and iron, and priorities for future research. Ann Nutr Metab 59:5–9
63. Gould JF, Smithers LG, Makrides M (2013) The effect of maternal omega-3 (n-3) LCPUFA supplementation during pregnancy on early childhood cognitive and visual development: a systematic review and meta-analysis of randomized controlled trials. Am J Clin Nutr 97:531–544
64. Campoy C, Escolano-Margarit MV, Anjos T, Szajewska H, Uauy R (2012) Omega 3 fatty acids on child growth, visual acuity and neurodevelopment. Br J Nutr 107(Suppl 2):S85–S106
65. Dziechciarz P, Horvath A, Szajewska H (2010) Effects of n-3 long-chain polyunsaturated fatty acid supplementation during

pregnancy and/or lactation on neurodevelopment and visual function in children: a systematic review of randomized controlled trials. J Am Coll Nutr 29:443–454
66. Grantham-McGregor S and Ani C (2001) A review of studies on the effect of iron deficiency on cognitive development in children. J Nutr 131:649S–666S. discussion 666S–668S
67. Sachdev H, Gera T, Nestel P (2005) Effect of iron supplementation on mental and motor development in children: systematic review of randomised controlled trials. Public Health Nutr 8:117–132
68. van den Briel T, West CE, Bleichrodt N, van de Vijver FJ, Ategbo EA, Hautvast JG (2000) Improved iodine status is associated with improved mental performance of schoolchildren in Benin. Am J Clin Nutr 72:1179–1185
69. Best C, Neufingerl N, Del Rosso JM, Transler C, van den Briel T, Osendarp S (2011) Can multi-micronutrient food fortification improve the micronutrient status, growth, health, and cognition of schoolchildren? A systematic review. Nutr Rev 69:186–204
70. Azizi F, Kalani H, Kimiagar M, Ghazi A, Sarshar A, Nafarabadi M, Rahbar N, Noohi S, Mohajer M, Yassai M (1995) Physical, neuromotor and intellectual impairment in non-cretinous schoolchildren with iodine deficiency. Int J Vitam Nutr Res 65:199–205
71. Iannotti LL, Tielsch JM, Black MM, Black RE (2006) Iron supplementation in early childhood: health benefits and risks. Am J Clin Nutr 84:1261–1276
72. Beard JL (2008) Why iron deficiency is important in infant development. J Nutr 138:2534–2536
73. Lozoff B, Jimenez E, Hagen J, Mollen E, Wolf AW (2000) Poorer behavioral and developmental outcome more than 10 years after treatment for iron deficiency in infancy. Pediatrics 105:E51
74. Falkingham M, Abdelhamid A, Curtis P, Fairweather-Tait S, Dye L, Hooper L (2010) The effects of oral iron supplementation on cognition in older children and adults: a systematic review and meta-analysis. Nutr J 9:4
75. DiGirolamo AM, Ramirez-Zea M (2009) Role of zinc in maternal and child mental health. Am J Clin Nutr 89:940S–945S
76. Bhatnagar S, Taneja S (2001) Zinc and cognitive development. Br J Nutr 85(Suppl 2):S139–S145
77. Louwman MW, van Dusseldorp M, van de Vijver FJ, Thomas CM, Schneede J, Ueland PM, Refsum H, van Staveren WA (2000) Signs of impaired cognitive function in adolescents with marginal cobalamin status. Am J Clin Nutr 72:762–769
78. Nilsson TK, Yngve A, Bottiger AK, Hurtig-Wennlof A, Sjostrom M (2011) High folate intake is related to better academic achievement in Swedish adolescents. Pediatrics 128:e358–e365
79. Breimer LH and Nilsson TK (2012) Has folate a role in the developing nervous system after birth and not just during embryogenesis and gestation? Scand J Clin Lab Invest 72:185–191
80. Bonatto F, Polydoro M, Andrades ME, Conte da Frota ML Jr, Dal-Pizzol F, Rotta LN, Souza DO, Perry ML, Fonseca Moreira JC (2006) Effects of maternal protein malnutrition on oxidative markers in the young rat cortex and cerebellum. Neurosci Lett 406:281–284
81. Grantham-McGregor S, Baker-Henningham H (2005) Review of the evidence linking protein and energy to mental development. Public Health Nutr 8:1191–1201
82. Koletzko B, von Kries R, Closa R, Escribano J, Scaglioni S, Giovannini M, Beyer J, Demmelmair H, Gruszfeld D, Dobrzanska A, Sengier A, Langhendries JP, Rolland Cachera MF, Grote V (2009) Lower protein in infant formula is associated with lower weight up to age 2 y: a randomized clinical trial. Am J Clin Nutr 89:1836–1845
83. Ilcol YO, Ozbek R, Hamurtekin E, Ulus IH (2005) Choline status in newborns, infants, children, breast-feeding women, breast-fed infants and human breast milk. J Nutr Biochem 16:489–499
84. Willatts P, Forsyth JS (2000) The role of long-chain polyunsaturated fatty acids in infant cognitive development. Prostaglandins Leukot Essent Fatty Acids 63:95–100
85. Richardson AJ, Ross MA (2000) Fatty acid metabolism in neurodevelopmental disorder: a new perspective on associations between attention-deficit/hyperactivity disorder, dyslexia, dyspraxia and the autistic spectrum. Prostaglandins Leukot Essent Fatty Acids 63:1–9
86. Simopoulos AP (2010) Genetic variants in the metabolism of omega-6 and omega-3 fatty acids: their role in the determination of nutritional requirements and chronic disease risk. Exp Biol Med (Maywood) 235:785–795
87. Hibbeln JR, Davis JM, Steer C, Emmett P, Rogers I, Williams C, Golding J (2007) Maternal seafood consumption in pregnancy and neurodevelopmental outcomes in childhood (ALSPAC study): an observational cohort study. Lancet 369:578–585
88. Morales E, Bustamante M, Gonzalez JR, Guxens M, Torrent M, Mendez M, Garcia-Esteban R, Julvez J, Forns J, Vrijheid M, Molto-Puigmarti C, Lopez-Sabater C, Estivill X, Sunyer J (2011) Genetic variants of the FADS gene cluster and ELOVL gene family, colostrums LC-PUFA levels, breastfeeding, and child cognition. PLoS ONE 6:e17181
89. Fergusson DM, Beautrais AL, Silva PA (1982) Breast-feeding and cognitive development in the first seven years of life. Soc Sci Med 16:1705–1708
90. Horwood LJ, Fergusson DM (1998) Breastfeeding and later cognitive and academic outcomes. Pediatrics 101:E9
91. Lauzon-Guillain B, Wijndaele K, Clark M, Acerini CL, Hughes IA, Dunger DB, Wells JC, Ong KK (2012) Breastfeeding and infant temperament at age three months. PLoS ONE 7:e29326
92. Kafouri S, Kramer M, Leonard G, Perron M, Pike GB, Richer L, Toro R, Veillette S, Pausova Z and Paus T (2013) Breastfeeding and brain structure in adolescence. Int J Epidemiol 42:150–159
93. EFSA Panel on Dietetic Products NaAN (2011) Scientific Opinion on the substantiation of health claims related to docosahexaenoic acid (DHA), eicosapentaenoic acid (EPA) and brain, eye and nerve development (ID 501, 513, 540), maintenance of normal brain function (ID 497, 501, 510, 513, 519, 521, 534, 540, 688, 1323, 1360, 4294), maintenance of normal vision (ID 508, 510, 513, 519, 529, 540, 688, 2905, 4294), maintenance of normal cardiac function (ID 510, 688, 1360), "maternal health; pregnancy and nursing" (ID 514), "to fulfil increased omega-3 fatty acids need during pregnancy" (ID 539), "skin and digestive tract epithelial cells maintenance" (ID 525), enhancement of mood (ID 536), "membranes cell structure" (ID 4295), "anti-inflammatory action" (ID 4688) and maintenance of normal blood LDL-cholesterol concentrations (ID 4719) pursuant to Article 13(1) of Regulation (EC) No 1924/2006. EFSA Journal 9, 2078
94. Schulzke SM, Patole SK and Simmer K (2011) Long-chain polyunsaturated fatty acid supplementation in preterm infants. Cochrane Database Syst Rev CD000375
95. Benton D, Kallus KW, Schmitt JA (2005) How should we measure nutrition-induced improvements in memory? Eur J Nutr 44:485–498
96. Bellisle F (2004) Effects of diet on behaviour and cognition in children. Br J Nutr 92(Suppl 2):S227–S232
97. Burgard P (2003) Critical evaluation of the methodology employed in cognitive development trials. Acta Paediatr 92:6–10

98. Hughes D, Bryan J (2003) The assessment of cognitive performance in children: considerations for detecting nutritional influences. Nutr Rev 61:413–422
99. Schmitt JA, Benton D, Kallus KW (2005) General methodological considerations for the assessment of nutritional influences on human cognitive functions. Eur J Nutr 44:459–464
100. Crawford JR, Garthwaite PH, Howell DC (2009) On comparing a single case with a control sample: an alternative perspective. Neuropsychologia 47:2690–2695
101. Tomalski P, Johnson MH (2010) The effects of early adversity on the adult and developing brain. Curr Opin Psychiatry 23:233–238
102. Nelson CA, Monk CS (2001) Handbook in developmental cognitive neuroscience. MIT Press, Cambridge, MA, pp 125–136
103. Deregnier RA, Nelson CA, Thomas KM, Wewerka S, Georgieff MK (2000) Neurophysiologic evaluation of auditory recognition memory in healthy newborn infants and infants of diabetic mothers. J Pediatr 137:777–784
104. Rosales FJ, Reznick JS, Zeisel SH (2009) Understanding the role of nutrition in the brain and behavioral development of toddlers and preschool children: identifying and addressing methodological barriers. Nutr Neurosci 12:190–202
105. Paus T (2010) Population neuroscience: why and how. Hum Brain Mapp 31:891–903
106. White T, El Marroun H, Nijs I, Schmid M, van der Lugt A, Wielopolki P, Jaddoe V, Hofman A, Krestin GP, Tiemeier H and Verhulst FC (2013) Pediatric population-based neuroimaging and the Generation R Study: the intersection of developmental neuroscience and epidemiology. Eur J Epidemiol 28:99–111
107. Cade JE, Burley VJ, Warm DL, Thompson RL, Margetts BM (2004) Food-frequency questionnaires: a review of their design, validation and utilisation. Nutr Res Rev 17:5–22
108. Margetts BM, Nelson M (1997) Concepts in nutrition epidemiology. Oxford University Press, Oxford
109. Williams C, Birch EE, Emmett PM, Northstone K (2001) Stereoacuity at age 3.5 y in children born full-term is associated with prenatal and postnatal dietary factors: a report from a population-based cohort study. Am J Clin Nutr 73:316–322
110. Northstone K, Emmett PM (2008) Are dietary patterns stable throughout early and mid-childhood? A birth cohort study. Br J Nutr 100:1069–1076
111. Wirfalt E, Midthune D, Reedy J, Mitrou P, Flood A, Subar AF, Leitzmann M, Mouw T, Hollenbeck AR, Schatzkin A, Kipnis V (2009) Associations between food patterns defined by cluster analysis and colorectal cancer incidence in the NIH-AARP diet and health study. Eur J Clin Nutr 63:707–717
112. Cheong JL, Hunt RW, Anderson PJ, Howard K, Thompson DK, Wang HX, Bear MJ, Inder TE, Doyle LW (2008) Head growth in preterm infants: correlation with magnetic resonance imaging and neurodevelopmental outcome. Pediatrics 121:e1534–e1540
113. Cooke RW, Foulder-Hughes L (2003) Growth impairment in the very preterm and cognitive and motor performance at 7 years. Arch Dis Child 88:482–487
114. Neubauer AP, Voss W, Kattner E (2008) Outcome of extremely low birth weight survivors at school age: the influence of perinatal parameters on neurodevelopment. Eur J Pediatr 167:87–95
115. Frisk V, Amsel R, Whyte HE (2002) The importance of head growth patterns in predicting the cognitive abilities and literacy skills of small-for-gestational-age children. Dev Neuropsychol 22:565–593
116. Group WMGRS (2007) WHO child growth standards: Methods and development: Head circumference-for-age, arm circumference-for-age, triceps skinfold-for-age and subscapular skinfold-for-age. WHO Press, Geneva
117. Group WMGRS (2009) WHO child growth standards: methods and development: growth velocity based on weight, length and head circumference. WHO Press, Geneva
118. Ebbeling CB, Pawlak DB, Ludwig DS (2002) Childhood obesity: public-health crisis, common sense cure. Lancet 360:473–482
119. Erickson SJ, Robinson TN, Haydel KF, Killen JD (2000) Are overweight children unhappy?: body mass index, depressive symptoms, and overweight concerns in elementary school children. Arch Pediatr Adolesc Med 154:931–935
120. Strauss RS (2000) Childhood obesity and self-esteem. Pediatrics 105:e15
121. Van Lieshout RJ, Taylor VH, Boyle MH (2011) Pre-pregnancy and pregnancy obesity and neurodevelopmental outcomes in offspring: a systematic review. Obes Rev 12:e548–e559
122. Cserjesi R, Molnar D, Luminet O, Lenard L (2007) Is there any relationship between obesity and mental flexibility in children? Appetite 49:675–678
123. Pauli-Pott U, Albayrak O, Hebebrand J, Pott W (2010) Association between inhibitory control capacity and body weight in overweight and obese children and adolescents: dependence on age and inhibitory control component. Child Neuropsychol 16:592–603
124. Delgado-Rico E, Rio-Valle JS, Gonzalez-Jimenez E, Campoy C, Verdejo-Garcia A (2012) BMI predicts emotion-driven impulsivity and cognitive inflexibility in adolescents with excess weight. Obesity (Silver Spring) 20:1604–1610
125. Verdejo-Garcia A, Perez-Exposito M, Schmidt-Rio-Valle J, Fernandez-Serrano MJ, Cruz F, Perez-Garcia M, Lopez-Belmonte G, Martin-Matillas M, Martin-Lagos JA, Marcos A, Campoy C (2010) Selective alterations within executive functions in adolescents with excess weight. Obesity (Silver Spring) 18:1572–1578
126. Lohman TG, Roche AF and Martorell R (1988) Champaigne, Champaigne
127. Ce WHO (1995) Physical status: the use and interpretation of anthropometry. WHO Tech Rep Ser 854:368–369
128. Hillman CH, Erickson KI, Kramer AF (2008) Be smart, exercise your heart: exercise effects on brain and cognition. Nat Rev Neurosci 9:58–65
129. Rasberry CN, Lee SM, Robin L, Laris BA, Russell LA, Coyle KK, Nihiser AJ (2011) The association between school-based physical activity, including physical education, and academic performance: a systematic review of the literature. Prev Med 52(Suppl 1):S10–S20
130. Tomporowski PD, Davis CL, Miller PH, Naglieri JA (2008) Exercise and children's intelligence, cognition, and academic achievement. Educ Psychol Rev 20:111–131
131. Maddison R, Ni Mhurchu C, Jiang Y, Vander Hoorn S, Rodgers A, Lawes CM, Rush E (2007) International Physical Activity Questionnaire (IPAQ) and New Zealand Physical Activity Questionnaire (NZPAQ): a doubly labelled water validation. Int J Behav Nutr Phys Act 4:62
132. Melanson EL Jr, Freedson PS (1996) Physical activity assessment: a review of methods. Crit Rev Food Sci Nutr 36:385–396
133. Welk GJ, Corbin CB, Dale D (2000) Measurement issues in the assessment of physical activity in children. Res Q Exerc Sport 71:S59–S73
134. Saris WH, Snel P, Baecke J, van Waesberghe F, Binkhorst RA (1977) A portable miniature solid-state heart rate recorder for monitoring daily physical activity. Biotelemetry 4:131–140
135. Troiano RP (2005) A timely meeting: objective measurement of physical activity. Med Sci Sports Exerc 37:S487–S489
136. Van Cauwenberghe E, Gubbels J, De Bourdeaudhuij I, Cardon G (2011) Feasibility and validity of accelerometer measurements to assess physical activity in toddlers. Int J Behav Nutr Phys Act 8:67
137. Calabro MA, Welk GJ, Eisenmann JC (2009) Validation of the SenseWear Pro Armband algorithms in children. Med Sci Sports Exerc 41:1714–1720

138. Janz KF, Lutuchy EM, Wenthe P, Levy SM (2008) Measuring activity in children and adolescents using self-report: PAQ-C and PAQ-A. Med Sci Sports Exerc 40:767–772
139. Treuth MS, Hou N, Young DR, Maynard LM (2005) Validity and reliability of the Fels physical activity questionnaire for children. Med Sci Sports Exerc 37:488–495
140. Glaser C, Lattka E, Rzehak P, Steer C, Koletzko B (2011) Genetic variation in polyunsaturated fatty acid metabolism and its potential relevance for human development and health. Matern Child Nutr 7(Suppl 2):27–40
141. Lattka E, Illig T, Koletzko B, Heinrich J (2010) Genetic variants of the FADS1 FADS2 gene cluster as related to essential fatty acid metabolism. Curr Opin Lipidol 21:64–69
142. Glaser C, Heinrich J, Koletzko B (2010) Role of FADS1 and FADS2 polymorphisms in polyunsaturated fatty acid metabolism. Metabolism 59:993–999
143. Lattka E, Eggers S, Moeller G, Heim K, Weber M, Mehta D, Prokisch H, Illig T, Adamski J (2010) A common FADS2 promoter polymorphism increases promoter activity and facilitates binding of transcription factor ELK1. J Lipid Res 51:182–191
144. Koletzko B, Lattka E, Zeilinger S, Illig T, Steer C (2011) Genetic variants of the fatty acid desaturase gene cluster predict amounts of red blood cell docosahexaenoic and other polyunsaturated fatty acids in pregnant women: findings from the Avon Longitudinal Study of Parents and Children. Am J Clin Nutr 93:211–219
145. Lattka E, Klopp N, Demmelmair H, Klingler M, Heinrich J, Koletzko B (2012) Genetic variations in polyunsaturated fatty acid metabolism–implications for child health? Ann Nutr Metab 60(Suppl 3):8–17
146. Lattka E, Rzehak P, Szabo E, Jakobik V, Weck M, Weyermann M, Grallert H, Rothenbacher D, Heinrich J, Brenner H, Decsi T, Illig T, Koletzko B (2011) Genetic variants in the FADS gene cluster are associated with arachidonic acid concentrations of human breast milk at 1.5 and 6 mo postpartum and influence the course of milk dodecanoic, tetracosenoic, and trans-9-octadecenoic acid concentrations over the duration of lactation. Am J Clin Nutr 93:382–391
147. Schaeffer L, Gohlke H, Muller M, Heid IM, Palmer LJ, Kompauer I, Demmelmair H, Illig T, Koletzko B, Heinrich J (2006) Common genetic variants of the FADS1 FADS2 gene cluster and their reconstructed haplotypes are associated with the fatty acid composition in phospholipids. Hum Mol Genet 15:1745–1756
148. Gieger C, Geistlinger L, Altmaier E, Hrabe de Angelis M, Kronenberg F, Meitinger T, Mewes HW, Wichmann HE, Weinberger KM, Adamski J, Illig T, Suhre K (2008) Genetics meets metabolomics: a genome-wide association study of metabolite profiles in human serum. PLoS Genet 4:e1000282
149. Caspi A, Williams B, Kim-Cohen J, Craig IW, Milne BJ, Poulton R, Schalkwyk LC, Taylor A, Werts H, Moffitt TE (2007) Moderation of breastfeeding effects on the IQ by genetic variation in fatty acid metabolism. Proc Natl Acad Sci USA 104:18860–18865
150. Steer CD, Davey Smith G, Emmett PM, Hibbeln JR, Golding J (2010) FADS2 polymorphisms modify the effect of breastfeeding on child IQ. PLoS ONE 5:e11570
151. Wright RO, Hu H, Silverman EK, Tsaih SW, Schwartz J, Bellinger D, Palazuelos E, Weiss ST, Hernandez-Avila M (2003) Apolipoprotein E genotype predicts 24-month bayley scales infant development score. Pediatr Res 54:819–825
152. Laanpere M, Altmäe S, Stavreus-Evers A, Nilsson TK, Yngve A, Salumets A (2010) Folate-mediated one-carbon metabolism and its effect on female fertility and pregnancy viability. Nutr Rev 68:99–113
153. Altmäe S, Stavreus-Evers A, Ruiz JR, Laanpere M, Syvanen T, Yngve A, Salumets A, Nilsson TK (2010) Variations in folate pathway genes are associated with unexplained female infertility. Fertil Steril 94:130–137
154. Frosst P, Blom HJ, Milos R, Goyette P, Sheppard CA, Matthews RG, Boers GJ, den Heijer M, Kluijtmans LA, van den Heuvel LP et al (1995) A candidate genetic risk factor for vascular disease: a common mutation in methylenetetrahydrofolate reductase. Nat Genet 10:111–113
155. Harmon DL, Woodside JV, Yarnell JW, McMaster D, Young IS, McCrum EE, Gey KF, Whitehead AS, Evans AE (1996) The common 'thermolabile' variant of methylene tetrahydrofolate reductase is a major determinant of mild hyperhomocysteinaemia. QJM 89:571–577
156. Pilsner JR, Hu H, Wright RO, Kordas K, Ettinger AS, Sanchez BN, Cantonwine D, Lazarus AL, Cantoral A, Schnaas L, Tellez-Rojo MM, Hernandez-Avila M (2010) Maternal MTHFR genotype and haplotype predict deficits in early cognitive development in a lead-exposed birth cohort in Mexico City. Am J Clin Nutr 92:226–234
157. Schmidt RJ, Hansen RL, Hartiala J, Allayee H, Schmidt LC, Tancredi DJ, Tassone F, Hertz-Picciotto I (2011) Prenatal vitamins, one-carbon metabolism gene variants, and risk for autism. Epidemiology 22:476–485
158. Ordovas JM, Corella D (2004) Nutritional genomics. Annu Rev Genomics Hum Genet 5:71–118
159. Muller M, Kersten S (2003) Nutrigenomics: goals and strategies. Nat Rev Genet 4:315–322
160. Afman LA, Muller M (2012) Human nutrigenomics of gene regulation by dietary fatty acids. Prog Lipid Res 51:63–70
161. Tanaka T, Shen J, Abecasis GR, Kisialiou A, Ordovas JM, Guralnik JM, Singleton A, Bandinelli S, Cherubini A, Arnett D, Tsai MY, Ferrucci L (2009) Genome-wide association study of plasma polyunsaturated fatty acids in the InCHIANTI Study. PLoS Genet 5:e1000338
162. Illig T, Gieger C, Zhai G, Romisch-Margl W, Wang-Sattler R, Prehn C, Altmaier E, Kastenmuller G, Kato BS, Mewes HW, Meitinger T, de Angelis MH, Kronenberg F, Soranzo N, Wichmann HE, Spector TD, Adamski J, Suhre K (2010) A genome-wide perspective of genetic variation in human metabolism. Nat Genet 42:137–141
163. Lenroot RK, Giedd JN (2011) Annual research review: developmental considerations of gene by environment interactions. J Child Psychol Psychiatry 52:429–441
164. Egger G, Liang G, Aparicio A, Jones PA (2004) Epigenetics in human disease and prospects for epigenetic therapy. Nature 429:457–463
165. He L, Hannon GJ (2004) MicroRNAs: small RNAs with a big role in gene regulation. Nat Rev Genet 5:522–531
166. Gabory A, Attig L, Junien C (2011) Epigenetic mechanisms involved in developmental nutritional programming. World J Diabetes 2:164–175
167. Roth TL, Sweatt JD (2011) Annual research review: epigenetic mechanisms and environmental shaping of the brain during sensitive periods of development. J Child Psychol Psychiatry 52:398–408
168. Attig L, Gabory A, Junien C (2010) Nutritional developmental epigenomics: immediate and long-lasting effects. Proc Nutr Soc 69:221–231
169. Lumey LH, Stein AD, Kahn HS, van der Pal-de Bruin KM, Blauw GJ, Zybert PA, Susser ES (2007) Cohort profile: the Dutch Hunger Winter families study. Int J Epidemiol 36:1196–1204
170. St Clair D, Xu M, Wang P, Yu Y, Fang Y, Zhang F, Zheng X, Gu N, Feng G, Sham P, He L (2005) Rates of adult schizophrenia following prenatal exposure to the Chinese famine of 1959–1961. JAMA 294:557–562

171. Steegers-Theunissen RP, Obermann-Borst SA, Kremer D, Lindemans J, Siebel C, Steegers EA, Slagboom PE, Heijmans BT (2009) Periconceptional maternal folic acid use of 400 microg per day is related to increased methylation of the IGF2 gene in the very young child. PLoS ONE 4:e7845
172. Tobi EW, Lumey LH, Talens RP, Kremer D, Putter H, Stein AD, Slagboom PE, Heijmans BT (2009) DNA methylation differences after exposure to prenatal famine are common and timing-and sex-specific. Hum Mol Genet 18:4046–4053
173. Leung BM, Wiens KP, Kaplan BJ (2011) Does prenatal micronutrient supplementation improve children's mental development? A systematic review. BMC Pregnancy Childbirth 11:12
174. Xie L, Innis SM (2008) Genetic variants of the FADS1 FADS2 gene cluster are associated with altered (n-6) and (n-3) essential fatty acids in plasma and erythrocyte phospholipids in women during pregnancy and in breast milk during lactation. J Nutr 138:2222–2228
175. Lippmann O (1969) Vision of young children. Arch Ophthalmol 81:763–775
176. Holmes JM, Beck RW, Repka MX, Leske DA, Kraker RT, Blair RC, Moke PS, Birch EE, Saunders RA, Hertle RW, Quinn GE, Simons KA, Miller JM (2001) The amblyopia treatment study visual acuity testing protocol. Arch Ophthalmol 119:1345–1353
177. Moke PS, Turpin AH, Beck RW, Holmes JM, Repka MX, Birch EE, Hertle RW, Kraker RT, Miller JM, Johnson CA (2001) Computerized method of visual acuity testing: adaptation of the amblyopia treatment study visual acuity testing protocol. Am J Ophthalmol 132:903–909