An overview of the NUTRIMENTHE project

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Summary
The NUTRIMENTHE project is in receipt of €5.9 million from the European Commission’s Seventh Framework Programme to study the effect of diet on the mental performance of children. The project is especially interested in the effect of B-vitamins, protein (in breast and formula milk), minerals and long-chain polyunsaturated fatty acids on the six main domains of mental performance. NUTRIMENTHE is also researching consumer perceptions of how diet affects mental performance and the economic consequence of improving mental performance. This article provides an insight into the results and progress made to date by the project.

Keywords: diet, mental performance, micronutrients, NUTRIMENTHE, nutrition, protein

Introduction
NUTRIMENTHE is a 5-year project part-funded by the European Commission’s Seventh Framework Programme for Research and Development that is investigating the effect of diet on the mental performance of children. Current evidence in this area of research is largely based on animal, retrospective studies and short-term intervention studies in humans, but the idea that the diet of mothers, infants and children could have an influence on long-term mental performance has major implications for public health practice, policy development and for our understanding of human biology. Several nutrients are of interest to NUTRIMENTHE, namely B-vitamins, minerals such as iron and zinc, protein (in breast and formula milk) and long-chain polyunsaturated fatty acids (LC-PUFAs), especially omega-3 fatty acids. NUTRIMENTHE is looking at the way that diet/nutrition affects mental performance in different age ranges, from pre-natal (early life programming) to childhood. The project is being co-ordinated by Professor Cristina Campoy of the University of Granada, Spain, and involves a multidisciplinary team of scientists from 20 organisations in Europe and the USA. The children taking part in the studies are drawn from large, well-characterised, population-based studies, including Generation R from Rotterdam and the Avon Longitudinal Study of Parents and Children from Bristol (ALSPAC). The Generation R cohort is being used to examine the effects of maternal dietary intake and nutritional status (folate and fatty acids) on cognition and behavioural development of children up to the age of 5. The ALSPAC cohort is being utilised to look at the interaction of fish intake during pregnancy and genetic variation.

Previously, ALSPAC has shown that children benefit from their mother’s consumption of fish during pregnancy by showing higher verbal IQ and pro-social behaviour compared with the children of women who ate no fish during pregnancy (Hibbeln et al. 2007). But the question is, which nutrients in fish mediate the effect? Fish contains many nutrients that could be responsible such as LC-PUFAs, iodine and vitamin D to name three – and through NUTRIMENTHE, this is being investigated further.

NUTRIMENTHE’s research plan also includes data from children participating within two randomised clinical intervention trials, which began during...
Framework Programme Five. One of these, NUHEAL (Nutraceuticals for a Healthier Life), was a 3-year study (completed in 2003) that considered the long-term effect of supplementation with either fish oil, folate, both or a placebo during pregnancy on neurodevelopment, potential allergies and cardiovascular risk during infancy and childhood. The other, CHOP (the European Childhood Obesity Project), investigated whether two types of infant formulae with differing protein content can influence the risk of childhood obesity. The long-term effects of both these interventions on mental performance are being followed up under the auspices of NUTRIMENTHE.

Two new intervention trials were set up after the start of NUTRIMENTHE. Namely, SIMBA (Study Investigating Mental Acuity effect of B-Vitamins in children) and a study involving patients with phenylketonuria (PKU). The SIMBA study examined whether the provision of B-vitamins improves cognition and behaviour in pre-school children. The PKU study provided defined amounts of docosahexaenoic acid (DHA) to school-aged children with PKU. These patients typically have an extremely low LC-PUFA intake and previous studies have established that certain neural functions, visual evoked potentials (VEPs) (Beblo et al. 2001), fine motor skills and coordination (Beblo et al. 2007) are improved by high doses of LC-PUFA. NUTRIMENTHE aims to take this further and to establish, for the first time, a cut-off value in PKU patients that would define the minimum DHA content required for optimal neural function.

The nutritional status of pregnant women and children may not only be influenced by diet, genetic polymorphisms may also be involved. With its interest in the role of LC-PUFAs in mental performance, NUTRIMENTHE is also looking at polymorphisms of genes in the fatty acid desaturase cluster (FADS), which encode the enzymes involved in fatty acid metabolism, to establish their role in relation to mental performance. Finally, NUTRIMENTHE has two further ongoing studies: one addressing consumer perception (parents and teachers) of the relationship between children’s diet and their mental performance, and the other being an examination of the economic consequences of improving mental performance for European populations as a whole.

Overall, the NUTRIMENTHE project is generating a vast quantity of data. Studies are taking place in seven countries and involve children of different ages (around 20,000 children). Data being collected includes assessment of dietary intake and the nutritional status of both children and pregnant women (i.e. for fatty acid and micronutrient level), as well as anthropometry, physical activity and brain scan data from the children participating. NUTRIMENTHE intends to link these measurements to the six main domains of mental performance; perception, psychomotor functions, memory, attention, language and executive functions. Consequently, the development of a harmonised battery of neuropsychological tests was crucial to the project to enable the comparison of results from the many different studies. Development of the test battery was not without its challenges, however, including the selection of appropriate tests, obtaining permission for use, translation and back translation in seven languages, as well as adaptation to different cultures. Once the harmonisation process was complete, psychiatrists and psychologists from NUTRIMENTHE were trained to administer the tests, which are now in use by the project partners.

**Progress**

Work published by NUTRIMENTHE to date adds to the growing evidence linking pre-natal nutrition to child health, particularly mental performance, and demonstrates how genetic variation in mothers and children affects the processing of LC-PUFAs. The following provides an insight into some of the results published to date.

**Folic acid supplementation during pregnancy and toddler behaviour**

It is well known that supplementation with folate during pregnancy can reduce the occurrence of neural tube defects, but information on the role of folate on subsequent neurodevelopment is scarce. NUTRIMENTHE has published research demonstrating that inadequate folate use during pregnancy is associated with a higher risk of behavioural problems in children at 18 months (Roza et al. 2010). Pregnant women were asked about their use of folate supplementation in pregnancy, whether it was taken before conception or sometime later during pregnancy, or not at all. Child behaviour was assessed by the Child Behaviour Checklist for toddlers, which is used to obtain standardised reports, by parents, of their child’s behaviour (Achenbach & Rescorla 2000). This checklist includes an assessment of whether a child is emotionally reactive, anxious, depressed, has sleep problems, attention problems or exhibits aggressive behaviour. In the current study, information on child behavioural problems was available from over 4000 toddlers. Findings showed that even when results were adjusted for confounding vari-
ables, inadequate folate use resulted in a higher risk of total behavioural problems.

**Maternal hypothyroxinemia and cognition in early childhood**

NUTRIMENTHE researchers have published the results of work looking at how maternal thyroid function might affect cognitive development in early childhood (Henrichs et al. 2010) as data relating maternal thyroid function to children’s cognitive development are sparse. The researchers looked in more detail at how verbal and non-verbal communication in young children is related to thyroid hormone levels in the blood of women during early pregnancy and in babies at birth. They found that severe lack of thyroid hormone (hypothyroxinemia) predicted a higher likelihood of expressive language delay at 18 and 30 months. Expressive language includes the ability to form sentences, use grammar correctly and to retell a story or event. A risk of non-verbal cognitive delay (block building, imitation, planning and organising) was also found. The researchers concluded that low levels of thyroid hormone in pregnant women can affect fetal brain development and put children at risk of expressive language delay.

**Improvement of neural function in children with phenylketonuria by supplementation with docosahexaenoic acid**

Phenylketonuria is one of the most common inborn errors of metabolism in Caucasian populations. It leads to impaired oxidation of the amino acid phenylalanine, and if left untreated, can lead to psychomotor and mental retardation. Once diagnosed, treatment involves strict limitation of dietary protein. As a consequence, blood concentrations of LC-PUFA, especially DHA, are low compared with omnivorous children. NUTRIMENTHE has examined neural function in 36 children with well-managed PKU before and after supplementation with a defined amount of DHA (15 mg/kg/day). Measurements of VEPs, coordination and fine motor skills (Rostock-Oseretsky Scale) were performed at baseline and 3 months. Both significantly improved after DHA supplementation in PKU children compared with non-PKU controls, which remained unchanged, suggesting that preformed omega-3 PUFAs are needed for neural normality in PKU children (Koletzko et al. 2009).

**Fatty Acid Desaturase (FADS) genotypes and fatty acid processing**

The FADS 1 and FADS 2 genes encode the delta-5 and delta-6 desaturase enzymes that are involved in the synthesis of omega-3 and omega-6 fatty acids. It is known that common single nucleotide polymorphisms (SNPs) in these genes are associated with plasma levels of LC-PUFAs such as arachidonic acid and DHA. NUTRIMENTHE is interested in 17 SNPs and has been discovering how FADS polymorphisms influence the way that fatty acids are processed during pregnancy and in breastfeeding. NUTRIMENTHE has found that genetic variants of FADS1 and FADS2, commonly found in the population, are associated with levels of fatty acids in the red blood cells of pregnant women, including DHA (Koletzko et al. 2011). In a further study, fatty acids were extracted from breast-milk at 1.5 and 6 months post-birth. The studies concluded that maternal FADS genotypes are associated with breastmilk concentrations of fatty acids, particularly the omega-6 fatty acids and arachidonic acid (Lattka et al. 2011). Thus, NUTRIMENTHE is showing that the supply of fatty acids during pregnancy and breastfeeding may depend not only on dietary supply but also on genetic variation.

**Consumer perceptions**

To date, there is little published research on parent’s perceptions of the relationship between children’s diet and their mental performance; hence, one of NUTRIMENTHE’s objectives is to examine this through a series of consumer surveys. These surveys are assessing the attitudes and beliefs of parents with regard to the effect of food and nutrition on children’s mental performance and indeed exploring what parents understand by the term ‘mental performance’. Published to date are the results of a qualitative interview study with 124 parents of children aged 4–10 years from four European countries: the UK, Spain, Germany and Hungary (Brands et al. 2012). The study examined whether parents believe there is a link between diet and mental performance and indeed they do. Parents spoke of mental performance in terms of concentration and attention, manifested by effects on mood and behaviour. Parents focused on a single domain of cognition, attention, which is the one most often used to assess nutritional influences on cognitive performance. The parents also categorised food as ‘good’ or ‘bad’, with positive effects associated with a healthy, balanced diet and negative effects associated with high sugar or high fat food. The work of NUTRIMENTHE’s consumer surveys is ongoing, but ultimately they should provide valuable input into the targeting of messages that help inform effective consumer decision-making.
Economic surveys

Successful promotion and support for interventions that have long-term programming effects requires resources, and societies will only invest if the achievements outweigh the costs. Many health economic studies have been performed with respect to narrowly defined health outcomes, but few have examined the broader socio-economic impact of health improvements in terms of worker productivity. Thus, NUTRIMENTHE aims to develop a model to evaluate the possible economic consequence of the long-term effects of improving mental performance. NUTRIMENTHE has begun this work by conducting systematic reviews of published results to establish which nutritional interventions have an effect on mental performance. So far, NUTRIMENTHE has published a systematic review of randomised controlled trials (RCTs) regarding iron supplementation of children and pregnant women (Szajewska et al. 2010). The objective of the review was to provide some resolution to the uncertainty regarding the effects of iron supplementation during pregnancy and/or early life on psychomotor and mental development. Five RCTs were included that addressed ‘iron only’ supplementation in non-anaemic, infants and children up to the age of 3 years. Evidence from the RCTs included in the review suggested that iron supplementation may positively influence a child’s psychomotor development, whereas it does not seem to alter their mental development or behaviour. In the future, the Economic Survey work will focus on using the economic model being developed to perform analysis of the data being generated in other NUTRIMENTHE studies, beginning with the results emerging from the ALSPAC cohort.

NUTRIMENTHE in the future

NUTRIMENTHE intends to quantify the effects of nutrition on mental performance and behaviour, and to assess the risks and benefits of differing nutrition in various age groups. From a wider European perspective, the project will increase the knowledge and awareness of parents, health professionals, teachers and food producers on how diet influences mental performance.

NUTRIMENTHE is about to enter its final year of funding and, although there is still much to achieve, the project continues to make good progress. Regular meetings between the project partners have led to a very integrated consortium and a friendly working atmosphere. New lines of research, leading to new deliverables, have been opened since the original proposal was written, which will serve to enrich the final content and results.

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Conflict of interest

The author has no conflict of interest to disclose.

NUTRIMENTHE project partners

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