Nutrition and cognition: meeting the challenge to obtain credible and evidence-based facts

Jeroen AJ Schmitt

Nutrition provides a practical and appealing approach to cognitive enhancement, including the modulation of long-term cognitive processes such as neurodevelopment and neurodegeneration. An abundance of promising nutritional influences on cognition have been identified, but many long-term effects remain to be confirmed by data from randomized controlled trials (RCTs). The current article provides a general outline of various factors that hamper the demonstration of causal long-term nutritional effects on cognition by RCTs and advocates the development of methodological solutions to enable substantiation in future RCTs.

INTRODUCTION

The notion that what humans eat – or refrain from eating – may have an important effect on cognitive abilities is widespread and highly appealing to a large part of the population. The desire to optimize cognitive functioning is present at all stages of life: from parents' wishes to support their children's cognitive development to adults and older adults seeking protection or alleviation from short-term or long-term cognitive decline. This has spurred the off-label use of certain prescription drugs, mostly stimulants such as methylphenidate or modafinil,[1,2] as well as numerous nutritional or herbal supplements aimed at promoting or preserving cognitive performance levels. Although some excellent scientific work aimed at qualifying and quantifying the effects of specific nutritional factors on cognition has been carried out, many of the proposed nutritional influences are hitherto poorly characterized and substantiated.[3]

The attractiveness of cognition enhancement and the associated public demand this generates has led to a wide range of nutritional and nutraceutical products with vague, unsubstantiated, and sometimes misleading promises and claims.[4] Tightening of claims regulation for such products, through, for example, the new European Union health claim legislation,[5] not only protects the consumer, but also creates a powerful drive to investigate and substantiate nutritional influences on cognition according to the strictest scientific criteria. Banning unsubstantiated claims and communications will eliminate false competition and allow research and development–driven food and ingredient companies to strengthen their research efforts.

LONG-TERM EFFECTS OF NUTRITION ON COGNITION

Nutrition essentially delivers four main classes of functional compounds that may affect brain functioning after absorption. Food provides energy for the brain (essentially glucose), building blocks (e.g., lipids and amino acids), and micronutrients for enzymatic and endocrine processes (e.g., iron, zinc, B vitamins, iodine) and is a source of bio- or psychoactive molecules that can exert a multitude of brain-relevant actions.[6,7] In addition, the organoleptic properties of food – such as taste, smell, and texture – may modulate cognition and mood directly.[6,8]

The acute and subchronic effects of single nutritional components on human cognition are relatively straightforward to investigate using available psychopharmacological and neuropsychological methods and tools. The acute effects of, for example, caffeine[9,10] and glucose[11,12] have been well documented over the past decades, but great challenges emerge when addressing the longer-term

Affiliations: *JAJ Schmitt* is with the Cognitive Sciences Group, Nestlé Research Center, Lausanne, Switzerland, and Brain Sciences Institute, Swinburne University, Melbourne, Australia.

Correspondence: ILSI Europe a.i.s.b.l., Av. E Mounier 83, box 6, 1200 Brussels, Belgium. E-mail: publications@ilsieurope.be, Phone: +32-2-771-00-14, Fax: +32-2-762-00-44.

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influences of nutrition on cognition, such as promotion of neurodevelopment or primary prevention of normal and pathological cognitive aging.

Long-term cognitive benefits of a particular nutritional factor are, by definition, discernable only after a significant delay, often spanning years or decades. These benefits may occur after continuous intake of nutritional components during that period or as a result of a previous shorter-duration exposure in, for example, a critical period. The former notion is illustrated by Benton[13] in the present supplement. He proposes and discusses the intriguing concept of accumulation of cognitive reserve during development as a means of decreasing the risk of cognitive decline during aging and the role for nutrition in building and maintaining cognitive reserve throughout life. The latter situation could be linked to a "cognitive programming" concept; Kussmann et al.[14] coined this term to capture how the history of environmental influences, including nutrition, may affect cognitive performance later in life, possibly via epigenetic mechanisms. Both scenarios would require randomized controlled trials (RCTs) to incorporate (extremely) long follow-up periods. Inevitable individual variations in a multitude of lifestyle, dietary, and environmental influences over the course of the study period, which may all interact with the intervention or independently modify the cognitive outcomes, greatly complicates the disentanglement of the pure effect of the nutritional intervention.

When studying the potential long-term effects of nutrition, valuable insights with regard to plausibility can be obtained through mechanistic, animal, and epidemiological approaches. These have yielded an abundance of hypotheses and mechanisms of potential nutrition and cognition interactions,[7] and although epidemiological results may contribute to the accumulation of evidence for causal relationships, as pointed out by Benton,[13] the demonstration of causal behavioral effects in humans in high-quality RCTs is essential to establish a strong evidence base for nutrition effects and associated dietary recommendations, communications, and claims.

The unfortunate reality is that there is a paucity of RCTs that confirm the proposed cognitive effects of numerous nutritional components, particularly for cognitive aging.[15] In another article in the present supplement, McCracken[16] nicely illustrates this gap by discussing the pattern of evidence for a relationship between vitamin B_{12} intake and cognitive performance in older adults. As she points out, lack of confirmation in RCTs may mean that the original hypothesis is incorrect or it may be related to inadequate methodology relating to the design or execution of the RCT.

METHODOLOGICAL ASPECTS OF ASSESSING LONG-TERM COGNITION EFFECTS

Dangour et al.[17] highlight one particular methodological aspect of primary prevention trails, namely, the selection and recruitment of the appropriate population. Using examples from large nutritional intervention studies, they discuss the risk of unintended recruitment bias and its implications and the potential of deliberate recruitment of at-risk populations to increase study sensitivity.

The need to identify at-risk populations seems to be one of the key factors in disentangling the effect that nutrition may have on health, including mental health. It has become clear that people can exhibit large variations in the magnitude and even the direction of observed health effects of nutritional habits or interventions. Although one-size-fits-all strategies with general nutritional recommendations may have an overall beneficial effect at an average population level, it is increasingly recognized that, at an individual level, such recommendations may not always exert the sought-after health benefits and may even have detrimental outcomes. Large interindividual differences in responsiveness have also hampered a clear substantiation of the potential health effects of nutritional factors and diets in intervention studies. The need to shift from general to more tailor-made nutritional advice has led to the quest for personalized nutrition, meaning nutrition suited to the specific need of the individual. Personalized nutrition can be defined at various levels, with increasing diagnostic challenges as we move closer to solutions that are truly individually tailored. Population segmentation criteria can range from demographic (e.g., age, sex) or other general characteristics (e.g., lifestyle, phenotype, performance level, current or past health status, family history), to nutritional state (e.g., deficiencies, body weight), to individual genetic properties (single genetic polymorphisms, multiple interacting genetic attributes, epigenetics).

Kussmann et al.[14] discuss the notion of using genetic characteristics to more specifically define target populations for nutritional interventions for cognitive benefits. Nutrigenomics, certainly when sets of genetic polymorphisms are combined with lifestyle characteristics are used as scores, emerges as a promising, yet still developing, method to identify at-risk populations as well as likely responders. The mid- to long-term modulation of gene expression through environmentally determined epigenetic changes adds a further layer of complexity to this field, but it may provide a key to understanding very long-term influences of nutrition on brain health.

In addition to issues relating to the target population, the sensitive measurement of relevant study outcomes is considered a key methodological aspect of RCTs. In terms of brain functioning, the outcomes that are most directly

associated with real-life benefits are actual performance measures, such as the ability to remember, concentrate, solve problems, understand, and judge information. General aspects including procedures, interpretation, pitfalls, and limitations of measuring performance using cognitive tests, as well as of mood assessments, have been described previously.[18–21] In this supplement, Wesnes[22] provides a comprehensive methodological overview of the characteristics and requirements of cognitive tests. The article highlights the importance of using appropriate measures and systems, as this is a prerequisite for the ability to accurately assess nutritional effects on cognition in RCTs. In addition to such performance outcomes, measuring the effects of nutritional intervention directly on brain structure, composition, and activation using various brain imaging techniques can be valuable. Although such findings are not readily translated into functional (behavioral) benefits, they may provide highly sensitive measures of nutritional effects. Also in this supplement, Paus[23] provides an introductory overview of the available brain imaging techniques and their applications and limitations for nutrition research, including RCTs.

When addressing the long-term effects of nutrition, the identification and validation of early predictive markers of the efficacy of the nutritional intervention and of modifiable risk factors is of the highest importance. Such markers would allow accurate prediction of the long-term end-benefits of the intervention without the need for extensive follow-up periods, thus enabling RCTs to deliver causal evidence. An overview of the status of (bio)marker research in the field of Alzheimer's disease has recently been published elsewhere,[24] but the topic is also briefly addressed in the workshop summary and commentary article by de Jager and Kovatcheva[25] in this supplement.

Further development of methods is essential to provide tools for more feasible, efficient, and sensitive RCTs, although the effective use of currently available techniques can already facilitate strong scientific accumulation of nutritional effects on cognitive functioning, as illustrated by Osendarp et al.[26] in their article on iron and mental development. They show how combining mechanistic and observational knowledge can be used to design tailor-made RCTs with a high sensitivity to detect a specific nutritional effect. Finally, de Jager and Kovatcheva[25] provide an integrated account of the discussions and key learnings of the workshop, including recommendations for future long-term intervention studies.

CONCLUSION

The evidence base for nutrition effects on cognition, or any other functional outcome, should not be different from that of any other life sciences discipline. Data from high-quality RCTs are an indispensable part of that evidence base. The complications of designing and executing long-term experimental nutritional trials pose a great challenge, but many of these problems are due to the specific methodological gaps that exist today. Method development, particularly related to sensitive and early measurement of relevant outcomes and the selection of appropriate study populations, is critical to enable the future construction of RCTS that are more feasible and sensitive.

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