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Title: Policy actions required to improve nutrition for brain health.

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Abstract

Brain health is a pressing global concern. Poor diet quality is a recognized major environmental risk factor for brain disorders and one of the few that is modifiable. There is substantial evidence that nutrition impacts on brain development and brain health across the life course. So why then is the full potential of nutrition not utilized to improve brain function? This commentary, which is based on discussions of the European Brain Research Area BRAINFOOD cluster[1], aims to highlight the most urgent research priorities concerning the evidence base in the area of nutrition and brain health and identifies three major issues that need to be addressed: 1) Increase causal and mechanistic evidence on the link between nutrition and brain health; 2) Produce effective messages/education concerning the role of food for brain health, and 3) Funding to support collaborative working across diverse stakeholders.

Costs associated with brain health conditions.

Non-communicable diseases associated with brain health, including neurological and mental health conditions such as dementia, depression, and obesity, are highly prevalent [1-3] and translate into an immense burden on society. For example, neurological and psychiatric disorders each account for more than 16 million disability-adjusted life years (DALYs), the loss of the equivalent of one year of full health on average.[3] The most debilitating conditions are stroke, Alzheimer's disease and other forms of dementia.[4] Stroke accounts for more than 1 million deaths per year and Alzheimer's disease (and other forms of dementia), and Parkinson's disease are among the top 3 causes of death due to neurological disorders in Europe.[3] Additionally, neurodevelopmental conditions such as Attention-deficit Hyperactivity Disorder (ADHD) and Autism Spectrum Disorder and mental health conditions such as substance use disorders, depressive disorders, anxiety disorders and schizophrenia are the leading causes of disability.[3] Population ageing and growth is predicted to drive large increases in the number of individuals affected by dementia globally.[4] Treating brain health conditions is also costly. For example, brain health conditions account for 35% of Europe's total disease burden with a yearly cost of almost €800 billion, which likely is an underestimation.[5]

Overweight and obesity both provide a risk for metabolic health but also for brain health and are increasing at a rapid rate globally.[6] Moreover, overweight and obesity are increasingly prevalent in children. Of particular concern is the rapidly growing number of women becoming pregnant whilst having overweight or obesity which can have serious long-term consequences for their children's metabolic and brain health.[7] At the same time, the widespread increase in food insecurity [8] poses significant challenges for brain health due to its negative impact on nutritional status and mental health.[9] The triple burden of malnutrition (i.e., overnutrition and obesity, undernutrition, and micronutrient deficiencies) reaches beyond health, since individuals fail to reach their full potential in terms of wider economic and societal contribution.[10] These challenges extend beyond the responsibility of the individual and can only be tackled by a serious overarching and sustained approach by governments, the food industry, and society working together.[11]

The potential of nutrition for brain health

Nutrition affects all aspects of brain development and brain function, which means that there is the potential to modify the diet and/or use nutritional interventions to prevent and treat brain health conditions. The field of nutritional psychiatry has taken off recently [12] and accumulating results of observational and intervention studies support a role for diet in depression onset and symptom management.[13] In addition, trials on clinical depression and in non-clinical populations suggest that addressing diet quality is an efficacious and cost-effective way to reduce symptoms.[14-17] Nutritional interventions have the potential to reduce cognitive decline and change the course of neurodegenerative diseases. For example, while there is no overall cure for dementia, there is a clear link between diet and the risk of dementia and dietary interventions have been shown to delay the onset or progression of the disease. Moreover, early intervention is more beneficial than late intervention.[18-21] However, a recent review of studies investigating the effect of consumption of food groups that are recommended as part of a healthy sustainable diet (e.g. wholegrain, fruits and vegetables) found that high-quality, strong *causal* evidence of the effects of these food groups on cognitive function across the life course is lacking.[22]

Nutritional interventions may hold great promise for intervention early in life.[23] The potential for nutrition to affect brain health across the life course when intervening in early life is high because important developmental processes are occurring, including neurogenesis and myelination that set the ability to develop cognitive and behavioural functions and individual resilience to later life challenges.[24] During pregnancy and lactation, nutritional interventions can affect both the mother and her offspring: as an example, as well as its well-documented effect on the prevention of neural tube disorders, supplementation with folic acid and multivitamin products before and during pregnancy lowers the risk of the offspring developing autism.[25,26] Moreover, both micronutrients and omega-3 fatty acid supplementation have been directly linked to a reduced likelihood of preterm birth, a known risk factor for neurodevelopmental problems with lifelong consequences.[27,28] However, more needs to be done, as supplementation programs, in Europe, have not reached their full potential.[28] For example, folic acid taken before pregnancy and in early pregnancy reduces the risk of a neural tube disorders. Yet, despite Public Health Initiatives across Europe recommending that women take 0.4 mg folic acid before becoming pregnant and during the first trimester, the prevalence of neural tube disorder pregnancies has not materially decreased in the EU since 1998. This result is in stark contrast to a dramatic fall observed in the USA, where fortification of flour with folic acid has become mandatory, concurrent with supplementation advice.[29] Also, there is generic advice, but no public health initiatives in Europe to highlight the relevance of adequate intake of omega-3 fatty acids via the diet and supplementation to reduce the risk of preterm birth, something that is currently being implemented in health care systems across Australia.[30] There is compelling evidence showing that the elimination of food additives, colorings and preservatives reduces symptoms of ADHD and that supplementation with omega-3 fatty acids and vitamins may decrease symptoms of ADHD and autism.[31,32] The efficacy of early dietary interventions is supported by pre-clinical studies. There is evidence that early dietary supplementation with essential micronutrients and omega-3 fatty acids can protect against the negative consequences of exposure to early-life adversity on brain structure and function.[33,34] This is key because early-life adversity is one of the main risk factors for developing psychopathology and metabolic disorders later in life.[35]

More broadly, early-life environment and experience have a major impact on the risk of developing brain and metabolic disorders later in life suggesting that such risks have an early-life origin. For example, there is an increasing prevalence of mothers suffering from mental health problems (e.g. depression, addiction, trauma) as well as overweight and obese pregnancies that are associated with a higher risk of pregnancy complications (including preterm birth) and importantly, lasting consequences for the later life health risks of the offspring.[36] These are a serious concern, as often such early environments cannot be avoided and thus require a holistic approach to break the intergenerational cycle. These examples emphasize the relevance of considering the interaction between nutrition and brain health from a longer-term perspective. Many brain health problems are associated with diet and lifestyle risk factors that have occurred or started much earlier in life.

Across all age groups, maintaining balanced energy intake is essential to avoid both harmful energy deficits from malnutrition and the negative impacts of obesity resulting from overnutrition. However, each age group has distinct nutritional needs that are vital in regulating cognitive function and it is recommended to employ different interventions at different life stages, as each stage is characterized by specific physiological changes and related health targets. For instance, in midlife supplementation via nutraceutical compounds might be useful to prevent low-grade inflammation and in older adulthood, combining a healthier lifestyle with energy restriction presents a practical approach to slowing cognitive decline.[37]

Nutritional interventions have the potential to be employed throughout life, and in some cases, they appear perhaps even preferable to classic medication in treating emerging conditions, with greater consumer acceptance and lower side effects. However, there are still some major gaps in our understanding of the potential for specific nutritional strategies at each life stage [33] and many questions that are yet to be answered, including which interventions work, for whom and how best to translate the results of observational studies and experimental models into effective trials that provide more high-quality causal evidence for a role of nutrition in improving brain health.

How best to demonstrate the impact of nutrition on brain health?

There are many methodological challenges associated with the design and implementation of studies to test the effects of nutritional interventions on brain health, including issues with ensuring intervention adherence and blinding as well as the specific composition, and mode of diet delivery, that have been discussed in detail elsewhere. [12] Here we outline some specific issues for consideration as the evidence base builds.

Importance of understanding mechanisms.

The mechanisms of action associating diet with mental health outcomes are complex, interrelated and impinge on multiple biological pathways. Diet can have an important effect on several processes and mechanisms involving inflammatory markers, oxidative stress, mitochondrial function, and neuroendocrine effectors.[38] Evaluating which dietary components are beneficial for an individual requires greater mechanistic insight into individual genetic and environmental contexts to exploit the potential for food e.g. to reduce inflammation and oxidative stress while improving neuroendocrine function in response to everyday challenges.

Furthermore, epigenetic mechanisms are potentially involved in the long-term effects of dietary intake as well as in the intergenerational transmission of basic mechanisms and behaviors underlying food choices and susceptibility to mental disorders.[39] In addition, there is a growing appreciation of the role of the microbiome and microbial metabolites in shaping brain and behavior and the pathways of gut-brain signalling are being resolved.[40-42] Conversely, diet is one of the key factors that shape the microbiome composition across the lifespan.[43] The breadth of action of each specific nutrient and the complexity of interactions of various nutrients with the microbiome make disentangling the direct and indirect effects of nutrition on brain function and the specific neurobiological mechanisms involved challenging.[37,44] A novel framework to develop and evaluate the evidence base of how nutrients impact the brain is thus required.

Importance of stratification.

Studies to investigate possible beneficial effects of specific nutrients need to address perceived or anticipated nutrient gaps due to health issues, the diet or the environment as well as investigate the effects of specific nutrient levels above the recommended intake. This ideally should be studied in the context of the background diet that may be adequate or not in providing these nutrients. For example, in a gestational diabetes mellitus study, differences in the effect sizes of interventions were related to the background diet, which varied considerably in carbohydrate intake levels.[45,46] Many of the nutrients that may benefit brain health may already be an integral part of our diet, yet, depending on the habitual diet, intake levels may vary considerably. It has recently been shown that individuals with a balanced diet pattern, as estimated from a large data set of food preferences across a range of food categories, show better mental health and superior cognitive functions relative to other dietary patterns e.g. high protein and low fibre dietary pattern.[47] Nutrient requirements vary due to individual health, life stage, and lifestyle. Thus, individual nutrient needs are driven by physical and psychological health, habitual diet and lifestyle, and differ across the life course and according to the environment and challenges encountered.[48-50] In addition, nutrients serve as building blocks as well as acting as signaling molecules, providing the energy to perform daily tasks whilst maintaining body homeostasis. Recommendations for adequate intake of nutrients (recommended dietary allowance) are designed to cover the needs of 97% of the population, but given the normal distribution of individual requirements consequently overestimate the required intakes for most individuals to prevent deficiency at a population level. NHANES data suggests that actual sufficiency is closer to 70% of the population, highlighting the need to focus on deficiencies pertinent to specific target groups rather than at population level.[51] Specific subgroups (e.g., individuals with specific genetic vulnerabilities) may show a different response to a particular intervention compared to others and effects on a specific brain health domain may only be visible in a vulnerable population. This vulnerability could be determined by nutritional status (e.g., deficiency or insufficiency) or health status e.g., supplementation is most effective in treating deficiency in disease states. Ultimately, some recommendations may need to be stratified and personalized, while other recommendations may be beneficial for larger groups of people. However, personalisation is not without challenges including the implementation of (widespread) screening that may have ethical limitations and prove costly to implement.

Foods are not drugs.

Research into the efficacy of specific nutrients on brain health outcomes is more complex than studying drug efficacy.[52,53] The expectation that the research meets the standards set by regulatory bodies required for claims on the benefits of foods and nutrients does not acknowledge that the business models and the possible return on investment are entirely different from those of the pharmaceutical industry. With rare exceptions for specific nutrients and bioactives, food products cannot be commercially protected in the same way that new pharmaceutical molecules, designed to a specific receptor or mechanism of action, although safety assessment may require similar investments as for pharmaceutical compounds. Moreover, food manufacturers need to incorporate the nutrients of interest in an attractive and tasty product that can be marketed directly to the consumer and needs to be bought and consumed voluntarily regularly to achieve the beneficial effect. The required investment in research that is needed to test and show the efficacy of a specific product is substantial and unlikely to be matched by the potential financial return on investment. For example, improving intake of dietary fibre could have beneficial effects on many aspects of brain health, but the costs of running large-scale clinical trials that are not likely to lead to any proprietary knowledge may be prohibitive. The food industry has a role to play in building the evidence base but cannot act alone. An important consideration here is that for the food industry/private sector there is limited return on investment for research in this area, except for specific nutrients and bioactives or combinations thereof, where an application for a health claim is possible. Generation of the scientific evidence requires public funding. Harvesting the enormous health and cost-saving potential of nutritional interventions to maintain brain health and reduce the risk of brain diseases is a public health issue that is impossible to address without relevant public funding support, although the food industry has a moral obligation to work towards developing and providing healthy foods to the market. These challenges and complexities mean that nutrition in the context of brain health is an under-investigated scientific area, but also that it is under-researched as it has not (yet) been prioritized by funding bodies.

Importance of effective messaging.

Following dietary recommendations for health can be difficult but adherence may be improved if, in addition to knowing about distal benefits to physical health, people are aware that dietary change can have more immediate effects on mental and brain health. Nearly 9 in 10 adults said they would eat a healthier diet if they knew it would lower the risks of cognitive decline (87%), heart disease (88%), and diabetes (88%).[54] More than 60% of adults aged 40 and older said that they would eat more fish, less red meat, and lower their dairy fat intake if they knew it was good for their brain health.[52] A focus on the brain health benefits that accompany an improvement in diet quality rather than focusing on the benefits of weight loss may also be helpful for encouraging behavior change because a focus on weight can be stigmatizing.

Yet an issue is that consumers and patients are often faced with a barrage of conflicting and inconsistent findings about the potential (proximal) health effects of foods. This results in a lack of trust. In 2018, 80% of consumers reported coming across conflicting information about food and nutrition, which made them doubt their choices.[55] Social influencers are now a popular source of nutritional information, yet the advice provided is rarely founded on solid scientific evidence: at best it may be incomplete and incorrect, and at worst, harmful. The public may also receive differing advice from health-care providers on nutrition and health.

This may be in part because nutritional education in the medical curriculum is sparse, and the role of dietitians in the prevention and management of brain disorders is also limited. [56,57]

BRAINFOOD Priorities.

Recently there have been a number of initiatives in the US, Europe and Australia that testify the fact that diet and nutrition are important priorities for public health. Just as an example, in the US the "Food is medicine" Institute has been developed at Tufts University. The aim is to develop a set of food-based nutrition programs and interventions integrated into the healthcare system to advance specific health needs and health equity in different populations. Also, they are aiming to overcome one of the major drawbacks so far, which is the lack of large randomized clinical trials in different patient populations as well as estimating costs, cost-effectiveness, and effects on disparities of specific programs in addition to assessing public perceptions of the public for the subject. In Australia, the Food & Mood Centre has been founded by researchers also animating a specific Scientific Society: The International Society for Nutritional Psychiatry Research (ISNPR). In Europe, the initiative "Healthy Diet, Healthy Life (HDHL)" has been set up bringing together 17 countries that align research programming and fund new research to prevent or minimize diet-related chronic diseases (https://www.healthydietforhealthylife.eu/). Although not being directly linked to brain health, these programs have the merit to put diet and nutrition under the spotlight as major determinants of health. Within the European College of Neuropsychopharmacology (ECNP) a specific section on nutrition and mental health (Nutrition network) is present made up by many of the authors of this article. Overall, there is a surge of initiatives, both linked to scientific societies or Institutions or funding bodies and legislators that are attempting to align research education and policy in nutrition for brain health.

Given the potential of nutrition to support brain health, further investment in research to build a robust evidence base, in addition to education of health care professionals on this topic is urgently required. The link between a healthy, balanced diet and brain health calls for substantial action from policymakers to enable knowledge-building on diets that support brain health to make these accessible for all. The lack of consensus on the effects of diets and nutrients for brain health is in part related to the limited evidence base, since the number of high-quality studies that have been published to date is relatively small. With a few exceptions, most nutrient-brain health associations are driven by diet and lifestyle, meaning that the question of whether the effects of nutrition on the brain are independent or correlate of other healthy behaviours remains open. There is also a strong need for holistic, appropriate nutritional recommendations tailored to individual needs and age. Both the quality and strength of evidence need to be improved and disseminated in a clear, consistent, and accessible manner.

The most urgent research priorities in the BRAINFOOD area are:

1. **Identify nutrients and nutritional interventions that impact on brain health.**
   The transfer of findings from basic biomedical research into medical application is one of the major challenges in nutrition research. For specific nutrients or nutritional interventions where there is already a substantial evidence base, further trials are required to confirm the impact on brain health. The use of more stringent statistical

approaches in analyzing data from observational studies, such as Mendelian Randomization to control for hidden confounders would allow for (cautious) conclusions about causality to be drawn. Cohort research on clinical nutrition should systematically collect clinical data in databases and registries that are standardized and accessible at the individual level. Relevant and measurable patient-centered outcomes and appropriate study designs are needed, and international cooperation and multi-stakeholder engagement are key for success. The power of omics strategies (genetics, metabolomics, microbiomics, nutriomics) needs to be utilized to understand how individual differences in nutritional status and intake impact brain health. Systematic and interoperable data curation way would allow integration and scaling up of current levels of analysis, but this needs to be grounded in advances in technologies for a more robust and reliable assessment of diet to ensure data quality and reliability. The development of a Nutrition Research Infrastructure or Knowledge Platform enforcing FAIR principles, harmonization and standardization of study designs and data curation would strengthen networking between researchers and deliver relevant information to stakeholders, policymakers and the public in accessible and usable form.

2. **Identify and explore the neuronal circuits, cells and molecules linking nutrition with brain health.**
   We need to unravel which effects of nutrition are direct or indirect and additionally determine the relative contribution of hormonal, immune and microbiome systems. In addition, the contributions of single nutrients and how they act in combination need to be elucidated. For which nutrients or combinations are there sufficient molecular and cellular insights to explain the mechanism of action on brain health? We need to identify truly innovative approaches to better understand the relationship between nutrients and brain health and to integrate this with research on food palatability and taste in order to direct human food choice towards beneficial nutritional intake. A mechanistic understanding of how food impacts brain health will not only assist in identifying those at risk but also more convincingly explain why a healthy and balanced diet providing nutrients in adequate amounts is important for brain health.

3. **Bridge basic science mechanisms to clinical outcomes by identifying biomarkers.**
   While a large literature based on preclinical animal studies already exists, intervention studies investigating markers related to clinical outcomes are needed. Experimental Medicine studies in humans involve assessing the effects of controlled exposure to an intervention and identifying early-stage markers that predict clinical outcomes. Markers can include biological measures e.g., neurotransmitter levels, or neurocognitive measures e.g. brain imaging measures. Such studies should be employed to optimize the selection of nutrients that can then be tested in lengthy and more expensive randomized controlled trials.

Conclusion

Addressing the challenges and priorities in the brain food field will result in tremendous benefits for society but cannot be achieved without the support of policymakers. We, the BRAINFOOD cluster, therefore, ask the policymakers to act and call for more research funding. We have identified three major issues that need to be addressed:

1. **Increase causal and mechanistic evidence on the link between nutrition and brain health.** Intuitively, people know that food is important for health but the current scientific evidence causally linking a selected type of diet and/or specific nutraceuticals with protective/beneficial effects on brain health is not yet based on extensive randomised clinical trials.

2. **Produce effective messages/education concerning the role of food for brain health**. There is poor understanding of how nutrition supports and maintains brain health both by the general population and by health professionals. The lack of evidence-based advice is further complicated by confusing and exaggerated messaging in the popular press. Nutritional education should be much higher on the agenda of healthcare professionals and governmental bodies.

3. **Funding to support collaborative cross-sector working**. Healthy nutrition for the brain requires access to safe, nutritious, affordable and culturally appropriate diets, throughout life, for all citizens. This cannot be achieved without public, private, and community sectors working together to improve the food environment and strengthen the link between food and health for consumers.

[1] Footnote
BRAINFOOD Cluster Description: The European Brain Research Area project — EBRA, led by the European Brain Council - EBC - and together with 3 other EU initiatives (ERANET-NEURON, JPND, and Human Brain Project) was created as a catalysing initiative for brain research stakeholders to streamline and better coordinate brain research across Europe. BRAINFOOD is an EBRA cluster that aims to positively impact brain health by improving the nutrition of European citizens based on fundamental insights into the bidirectional links between brain health and nutrition. The Cluster has been built in the framework of the Nutrition Network of the European College of Neuropsychopharmacology (ECNP).

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Conflict of Interest

JB has been a consultant to / member of advisory board of / and/or speaker for Takeda, Roche, Medice, Angelini, Janssen, and Servier. EvdB is an employee of Nestlé Research, Produit de Nestlé SA, Lausanne, Switzerland. JC has received research funding from 4D Pharma, Cremo, Dupont, Mead Johnson, Nutricia, and Pharmavite; has been an invited speaker at meetings organized by Alimentary Health, Alkermes, Ordesa, and Yakult; and has served as a consultant for Alkermes and Nestle. LD has Current funding from: UKRI and WBANA; Consultancy with Hass Avocado Board, Mars; Positions: ILSI Europe Board member; ILSI Global Board member. All other authors have no conflict of interest to declare.

Author Contribution

All authors contributed to the conceptualization and writing of the manuscript.

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