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NuBrain: UK consortium for optimal nutrition for healthy brain ageing

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Abstract

With an ageing global population, there is an urgent need to identify effective strategies to maintain brain health across the life course and therein minimise the risk of age-related neurodegenerative disorders reaching a severe stage which may manifest as dementia. An increasing body of evidence indicates that nutrition is a modifiable lifestyle factor that can promote healthy brain ageing and reduce dementia risk. However, at present, little is known about which dietary patterns, foods and food bioactives influence brain function during ageing, and more research is required to identify at-risk individuals and population subgroups who are most likely to benefit from future nutritional intervention intended to promote healthier brain ageing. This article introduces the newly established Medical Research Council-funded NuBrain consortium, the vision of which is to provide a step change in research in the area by developing novel approaches and techniques to further understand the complex interactions between diet and brain health and how we can support appropriate behaviour changes in the population. NuBrain will form a new, sustainable and internationally field-leading research consortium with multidisciplinary and complementary areas of expertise to address the fundamental research challenges in this area.

Keywords: ageing, brain health, cognitive function, dementia, Mediterranean diet, nutrition

Introduction

Globally, the number of people aged 60 years and over is set to reach two billion by 2050 (Prince *et al.* 2015). As older people account for the majority of health and social services spending, an increasing population share will result in greater demand on services if not mitigated by healthy ageing (Beard & Bloom 2015). In recognition, the World Health Organization (WHO) has highlighted 'Ageing Well' as a priority public health message, whilst UK research bodies including the Medical Research Council (MRC), the National Institute for Health Research (NIHR) and UK Research and Innovation (UKRI) have identified healthy ageing as a priority research area.

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In most people, cognitive function – particularly aspects of memory, executive function, processing speed and reasoning – declines with age. However, in some people these declines can be accelerated by the presence of neurodegenerative brain diseases, such as Alzheimer's disease, which can progress to differing degrees of cognitive impairment or to dementia (Deary *et al.* 2009). It is now known that these neurodegenerative brain diseases start in midlife due to a host of genetic, lifestyle and environmental factors (Ritchie *et al.* 2015). Currently, dementia affects around 850 000 individuals in the UK and 47 million people worldwide, with an estimated annual global cost of approximately US$1 trillion (Prince *et al.* 2015). However, without intervention, dementia prevalence is projected to more than double by 2050, and the worldwide cost of dementia is anticipated to reach US $2 trillion by 2030 (Prince *et al.* 2015), placing a considerable burden on individuals, families and public health services (Livingston *et al.* 2017). Against this background, there is an urgent need to identify (1) at-risk individuals and (2) modifiable factors applied at critical periods across the life course for targeted interventions to support better brain health in our ageing population.

There is strong and growing evidence that nutrition throughout the life course has a profound impact on age-associated cognitive decline and represents a tractable target to modify individual cognitive health and population dementia burden (Scarmeas *et al.* 2018). However, more research is needed to understand fully which dietary patterns, foods and food bioactives influence brain function during ageing and, therefore, have potential for preventing, delaying or attenuating the neuropathological changes that can lead to dementia. In the MRC/NIHR *Review of Nutrition and Human Health Research* (MRC & NIHR 2017), the role of nutrition in brain development and ageing was highlighted as a target area to further understand how nutrition can support good cognitive function and mental wellbeing and maintain this into later life. Although there are several ongoing brain health initiatives (*e.g. EU Joint Programme – Neurodegenerative Disease Research*, *EU Human Brian Project*, *US BRAIN Initiative*, *China Brain Project*), none have nutrition at the centre of their research efforts. The vision of the NuBrain consortium is to provide a step change in research in the area by developing novel approaches and techniques to further understand the complex interactions between diet and brain health and how we can support appropriate behaviour change in the population. NuBrain will bring together a new research consortium with multidisciplinary and complementary areas of expertise to address this specific challenge. The aim is to build a sustainable, internationally field-leading consortium in nutrition and brain health which can collectively address the fundamental research challenges in this area.

Nutrition and healthy brain ageing

Nutrition has emerged as a modifiable lifestyle factor to promote healthy brain ageing and reduce dementia risk (Livingston *et al.* 2017). Current evidence, which is principally derived from observational studies, has identified numerous dietary factors associated with better cognitive performance, with cell and mouse models providing insights into underlying physiological and molecular mechanisms (Vauzour *et al.* 2017; Scarmeas *et al.* 2018). Nutritional compounds which have attracted attention for their potential to improve cognition include the *n*-3 fatty acid, docosahexaenoic acid (DHA) (Dyall 2015), B vitamins (Luchsinger *et al.* 2007; Lefèvre-Arbogast *et al.* 2016), plant-derived flavonoids (Commenges *et al.* 2000; Letenneur *et al.* 2007), vitamin D (Anastasiou *et al.* 2014) and, inconsistently, inorganic nitrate (Gilchrist *et al.* 2014; Shannon *et al.* 2017; Clifford *et al.* 2019). However, comprehensive longitudinal data, combining sensitive neural biomarkers (*e.g.* cognitive function, structural and metabolic neuroimaging and fluid samples) with state-of-the-art detailed nutrition profiling, are lacking. Such information is needed to gain insights at a mechanistic level to inform decisions about which nutritional interventions are likely to be most important at both a population and individual level as either risk or resilience factors for neurodegeneration and brain health, respectively. It is also important to understand the likely 'effect-size' to drive impact, as well as when in the life course such nutrition-disease interactions occur (either as risks or mitigations). It is proposed that the greatest benefits of better nutrition will be to mitigate the high risk of brain disease in subgroups, such as those with an *APOEe4* genotype, females or those with a high cardiovascular burden (who experience earlier dementia onset, lower disability-free life expectancy and high lifetime health and social care costs; Pontifex *et al.* 2018). However, associations between nutrition and brain health for other, perhaps more prevalent, population subgroups are not fully defined and are a research priority.

Unsurprisingly, given the likely additive or synergistic effect of individual foods and dietary compounds, specific dietary patterns modelled on the traditional

such as the Mediterranean diet (MedDiet) – which has long been considered a paragon of healthy eating – have emerged as being potentially effective at maintaining brain health during ageing (Petersson & Philippou 2016). The dietary pattern these days described as the MedDiet is a primarily plant-based dietary pattern, incorporating a high consumption of fruits, vegetables, legumes, nuts, seeds and unrefined grains. Fish is typically consumed in moderate amounts, whilst red meat, processed foods and sugar-sweetened products are consumed sparingly. In addition, olive oil is used as a principal cooking fat, whilst alcohol (typically red wine) is consumed in small-to-moderate amounts, usually as an accompaniment to meals (Bach-Faig *et al.* 2011). In observational studies, conducted mainly in the Mediterranean basin, high versus low adherence to a MedDiet has been associated consistently with improved cognition, reduced cortical atrophy (the gradual and progressive degeneration of the outer layer of the brain) and a 10–40% lower incidence of dementia (Petersson & Philippou 2016). In addition, results from the Navarra and Barcelona cohorts of the *Prevención con Dieta Mediterránea (PREDIMED)* randomised controlled trial (RCT) demonstrate that intervention with a MedDiet, which in this study was supplemented with additional extra virgin olive oil or nuts, can improve cognition and reduce the rate of cognitive decline (Martínez-Lapiscina *et al.* 2013, 2014; Valls-Pedret *et al.* 2015). Outside the Mediterranean basin, fewer studies have explored associations between MedDiet adherence and cognitive function or dementia risk. However, promisingly, recent analyses of the UK-based Lothian Birth Cohort (Corley *et al.* 2013; Luciano *et al.* 2017) and EPIC-Norfolk Cohort (Shannon *et al.* 2019) have demonstrated that higher adherence to the MedDiet is associated with reduced brain atrophy and better cognitive function across several domains. This suggests that, with correct implementation, the MedDiet could represent an effective dietary strategy to aid healthy brain ageing in non-Mediterranean countries such as the UK. Mechanistically, these effects may be related to favourable alterations in blood glucose and lipid profiles (Rodríguez-Rejón *et al.* 2014; Ros *et al.* 2014), decreased oxidative stress and inflammation (Mena *et al.* 2009; Urquiaga *et al.* 2010; Casas *et al.* 2014), augmented nitric oxide (NO) bioavailability (Siervo *et al.* 2018; Shannon *et al.* 2018) and modulation of the gut microbiome (Filippis *et al.* 2016; Tosti *et al.* 2018). In NuBrain, we will extend these encouraging initial findings using data from other large UK cohorts as outlined below (see Work Package 2).

In addition to poor nutrition, physical inactivity has emerged as an important determinant of cognitive function and accounts for approximately 20% of the population attributable risk (PARs) of Alzheimer's dementia in the UK and in other European and US populations (Norton *et al.* 2014). Together, physical inactivity and poor diets have been estimated to account for ~50% of Alzheimer's disease cases that can be attributed to modifiable risk factors (Norton *et al.* 2014). As the effects of diet and physical activity on cognitive health are likely to be additive, multi-domain interventions that include both of these elements have attracted attention in recent years. Of particular importance is the *Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability* (*FINGER*) trial (Ngandu *et al.* 2015), which assessed the cognitive effect of a diet based on Finnish nutrition recommendations, alongside exercise, cognitive training and monitoring of vascular risk in an 'at-risk' elderly Finnish cohort. Following a 2-year intervention period, cognitive performance, as assessed through the comprehensive neuropsychological test battery (NTB), was improved compared with control (Ngandu *et al.* 2015). The effects of a combined dietary and physical activity intervention for dementia risk reduction in a UK setting are currently being explored as part of the ongoing *MedEx Dementia Risk Reduction-UK* programme (MedEx_DRRUK 2017) with initial feasibility data collection due to be completed in 2020. This is discussed in more detail below (see Work Package 3).

The NuBrain consortium

The NuBrain consortium has been funded by the MRC UK Nutrition Research Partnership (NRP) Collaboration Award. The consortium will aim to address the challenge of optimal nutrition for healthy brain ageing through a number of key objectives. These objectives will be addressed through five work packages that include activities and feasibility studies utilising novel approaches and multidisciplinary expertise. By focussing on these objectives, the consortium will work collaboratively to advance understanding of the complex interactions between nutrition and brain health during ageing and to develop and test interventions to achieve behaviour change in individuals, in order to manifest substantial impact at the population level. The objectives of the collaboration are to:

(1) Create a strong, sustainable multidisciplinary UK collaboration and Virtual Centre of Excellence,

focussed on strengthening and developing nutrition and brain ageing research.
(2) Provide a supportive and open environment for early and mid-career researchers from multiple disciplines to develop new skills and expertise and to foster innovation in nutrition and brain ageing research.
(3) Utilise existing cohort data sets and new data collected using state-of-the-art biomarker and behaviour (in particular nutritional) capture approaches to identify the biological mechanisms underpinning potentially effective and specific nutritional and other lifestyle interventions for healthy brain ageing.
(4) Develop and validate tools for early identification of at-risk individuals and population subgroups who are most likely to benefit from future nutritional interventions intended to promote healthier brain ageing and reduce the population burden of dementias.
(5) Begin to explore the aetiology of cognitive decline and higher dementia burden in females with a view to developing sex-specific diagnostic approaches and effective nutrition interventions to mitigate this.
(6) Prepare to coordinate the implementation of the first large-scale, definitive UK intervention study (*MedEx*) to test the hypothesis that 'whole diet' interventions can prevent/delay cognitive loss and reduce dementia risk during ageing.
(7) Work with the UK food industry and retail, public health, government, charities and members of the public to explore translational approaches to behaviour change in food production, purchasing and consumption to promote healthy brain ageing.
(8) Disseminate key findings and outcomes of the collaboration to the academic community and other stakeholders, and encourage further multidisciplinary/cross-boundary research.

Work Package 1: Collaboration launch and consortium development

The first work package of NuBrain will focus on governance and the launch of the NuBrain collaboration. This will include establishment of the collaboration's Executive and Steering Group, and a range of launch events at different institutions for academics and industry partners. We will also arrange a half-day public engagement event in collaboration with VOICE (www.voice-global.org/), an organisation that aims to capture the public's experience, ideas, opinions and expectations about research, innovation and policy developments that affect their lives. Collectively, these activities will allow the collaboration to develop new ideas, encourage new players to engage with the collaboration, raise the profile of the initiative, inform the public of the current state of knowledge and gain valuable public perception and insight to help inform future research in the area. The consortium will also set up a NuBrain website to communicate the main aims, objectives, events and new findings of the collaboration.

As part of Work Package 1, the consortium will host a sandpit event for early career researchers (ECRs) to develop new ideas and approaches. Senior academics and representatives from industry, charity sector and public health will provide guidance and mentorship to the ECRs throughout the event leading to further mentoring opportunities for fellowship applications or inclusion on bids. The sandpit event (due to take place late 2020) will provide a supportive environment to encourage the development of novel pilot/feasibility study proposals in nutrition and brain ageing led by ECRs. Successful proposals will be funded by the NuBrain consortium for 12 months.

Work Package 2: Nutrition and brain ageing cohort analysis

This work package aims to utilise and improve the linkage between key platforms and cohorts, and to develop deeper phenotyping to understand better the potentially effective dietary and lifestyle interventions for healthy brain ageing in different target populations.

Epidemiological and clinical trial evidence has indicated a role for diet in both the increase and decrease of incident dementia, as well as the amelioration of the course of disease in the period before dementia onset (Livingston *et al.* 2017; Scarmeas *et al.* 2018). Study conclusions are not consistent however, perhaps because diet is a complex interplay of multiple nutritional components that may have differential effects on brain health at different time points in the life course of the individual and life cycle of neurodegenerative disease. A much clearer understanding of the mechanisms linking specific nutritional exposures and markers of neuronal and synaptic health is required to provide an empirical basis for further interventions, either at a public health or individual level, as part of a personal prevention plan.

We have direct access to the full data sets for European Prevention of Alzheimer's Dementia Consortium (EPAD) (Ritchie *et al.* 2016; Solomon *et al.* 2018) and PREVENT Dementia (Ritchie & Ritchie 2012). In each, there is detailed phenotyping of neurodegenerative biomarkers and nutritional status, with a combined sample size of over 3000 individuals (none with dementia at baseline), aged 40–90 years. Discoveries of mechanisms linking specific nutritional elements to markers of neurodegeneration can then be used as the basis for informed enquiry about links between diets containing these elements and the same markers in other data sets such as UK Biobank. The heterogeneity of the cohorts we will have access to in fact helps support understanding whether consistency is present. For example, establishing whether findings are replicated between different heterogeneous data sets will allow us to generate hypotheses about reasons for consistency or inconsistency of findings including differences in design and data. Further, the analyses of multiple cohorts, particularly when these are large and are heterogeneous such as EPAD (currently nine countries involved including several in the Mediterranean region) and UK Biobank, provide opportunities for subgroup investigations that may be informative for the identification of specific subgroups or life course stages where associations may operate differently. One critical line of enquiry is whether observations of an association between diet and nutrition and brain health in epidemiological studies are a direct effect on the brain or a downstream consequence of improvements in cardiovascular and cerebrovascular health or an effect on the metabolic syndrome and diabetes. Access to longitudinal data sets purposed specifically to look at brain changes that also contain extensive lifestyle and nutritional analysis (as well as potential confounders) will help address this question.

Work Package 3: Future development of nutrition and brain ageing interventions

The ongoing *MedEx_DRRUK* programme aims to conduct the first large scale UK-based dementia risk reduction RCT, establishing whether a behavioural intervention over 2–5 years, to promote a MedDiet with or without increased physical activity, can reduce cognitive decline and brain atrophy in 'at-risk' adults (Bundy & Minihane 2018). As part of phase 1 of the *MedEx_DRRUK*, which was funded by Alzheimer's Research UK, we are conducting the *MedEx1* feasibility study in three UK centres (Norwich, Birmingham and Newcastle). This 6-month trial with older, UK adults aged 55–74 years will investigate the feasibility of achieving behaviour change in a UK population 'at risk' of dementia. The intervention is delivered using an interactive web-based intervention on the 'Lifestyle, Eating, Activity and Planning' ($LEAP^2$) platform, plus food delivery and face-to-face group-based sessions. The primary outcome measures are feasibility and behavioural change in response to the interventions, evaluated by participant recruitment and retention on the trial, and changes in MedDiet Score and physical activity. Secondary outcomes (used to inform the design and powering of a main trial) are cognitive test performance (assessed on measures of global and domain-specific function, including memory and non-memory performance), neuroimaging (MRI to assess regional blood flow) and the QRISK2 score (calculated using demographic and clinical information including blood pressure, cholesterol concentration, body mass index and disease history; https://qrisk.org/2017/). In NuBrain, we will conduct *MedEx2* piloting and feasibility studies to inform future large scale interventions in this area.

Work Package 4: Industry, public health and policy engagement

Work Package 4 will organise workshops and focus groups with industry, food retailers, public sector organisations and local authorities to explore opportunities to develop translational approaches to encourage new product development and behaviour change in food purchasing and consumption to promote healthy brain ageing. As part of this work package, we will also develop links with policy makers and implementers.

Work Package 5: Dissemination, communication of collaborative activities and development of further funding bids

Work Package 5 will develop a range of dissemination and knowledge transfer activities with key stakeholders to share the outcomes from the NuBrain collaboration. This is of vital importance to maintain the profile of the consortium, inform future potential bids and to continue to attract new players to the research area. This will include the final annual meeting of the collaboration, the development of a toolkit of resources for public engagement and an industry-facing workshop in collaboration with Campden BRI. Importantly, we shall also use the knowledge and findings developed from the previous work packages to

design and prepare funding bids for future pragmatic and scalable nutritional interventions to test potential dietary interventions to maintain good brain health during ageing.

Conclusions

The NuBrain consortium will build a sustainable, internationally field-leading consortium in nutrition and brain ageing. The consortium will work collaboratively to advance understanding of the complex interactions between nutrition and brain health during ageing, and will develop and test interventions to achieve positive behaviour change that facilitates healthy brain ageing. Given the rapidly increasing prevalence and escalating cost of dementia and other age-related cognitive disorders, this work is urgently needed. The consortium welcomes new collaborators in any relevant field and should contact the authors of this paper for further information on collaborative opportunities.

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Author contributions

Emma Stevenson, Oliver M Shannon, Anne Marie Minihane, Ashley Adamson, Alistair Burns, Tom Hill, Falko Sniehotta, Graciela Muniz-Terrera and Craig W Richie contributed equally to the preparation and writing of this manuscript. *Members of the collaboration*: Professor Emma Stevenson, Newcastle University (Principal Investigator); Professor Craig Richie, University of Edinburgh (Co-Principal Investigator); Professor Anne Marie Minihane, University of East Anglia (Co-Investigator); Professor Ashley Adamson, Newcastle University (Co-Investigator), Professor Alistair Burns, University of Manchester (Co-Investigator); Professor Tom Hill, Newcastle University (Co-Investigator); Professor Falko Sniehotta, Newcastle University (Co-Investigator); Dr. Graciela Muniz-Terrera, University of Edinburgh (Co-Investigator); Dr. Oliver Shannon, Newcastle University (Post-doctoral researcher).

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