**Title: Diet, nutrition and the ageing brain: current evidence and new directions’**

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Globally populations are ageing. By 2050, it is estimated that there will be 2 billion people aged 60 years or over, of which 131 million are projected to be affected by dementia, while depression is predicted to be the second leading cause of disability worldwide by 2020. Preventing or delaying the onset of these disorders should therefore be a public health priority. There is some evidence linking certain dietary patterns, particularly the Mediterranean diet, with a reduced risk of dementia and depression. Specific dietary components have also been investigated in relation to brain health, with emerging evidence supporting protective roles for omega-3 polyunsaturated fatty acids (PUFAs), polyphenols, vitamin D and B-vitamins. At this time, the totality of evidence is strongest in support of a role for folate and the metabolically related B-vitamins (vitamin B12, vitamin B6 and riboflavin) in slowing the progression of cognitive decline and possibly reducing the risk of depression in ageing. Future studies incorporating new technologies, such as magnetic resonance imaging and magnetoencephalography, offer much promise in identifying effective nutrition interventions that could reduce the risk of cognitive and mental disorders. This review will explore the ageing brain and the emerging evidence linking diet and specific nutrients with cognitive function and depression in ageing, with the potential to develop strategies that could improve quality of life in our ageing population.

Keywords: Nutrition; Cognition; Depression; Ageing; B-vitamins

1. **Introduction**

Globally the population is ageing, with predictions that the number of people aged 60 years and over will reach up to 2 billion by 2050(1). An estimated 23% of the global burden of disease arises in older people and mental disorders are reported as the leading cause of disability and ill health(2). Dementia and depression are the most common of these disorders in ageing as identified by the WHO(3). Cognitive function declines with age, ranging in severity from mild cognitive impairment (MCI) to dementia, with up to 50% of those with MCI going on to develop dementia within 5 years(4). MCI can be defined as “cognitive decline greater than expected for an individual's age and education level but that does not interfere notably with activities of daily life”(4), whereas dementia interferes with activities of daily living (5). Dementia currently affects 46.8 million people worldwide and is projected to affect over 131 million people by 2050(6), whilst depression is anticipated to be the second leading cause of disability worldwide by 2020(7), with 22% of males and 28% of females over the age of 65 years affected by depression(8). The economic burden of cognitive decline and depression is profound. Experts have calculated that dementia will be a trillion dollar disease by 2018(6). Figures for depression are currently estimated at over €3 billion in Ireland(9) and £7.5 billion in England(7). With mental health considered to be one of the greatest global challenges(10), there is an urgent need to identify modifiable factors for targeted interventions to promote better brain health in our ageing populations. Epidemiological evidence supports a role for certain dietary factors in brain health, opening up new potential avenues for prevention of dementia and mental illness in ageing(11,12).

This review will explore the influence of ageing on brain health and the emerging evidence linking diet and specific nutrients with cognitive function and depression in ageing. The use of novel imaging technologies in nutrition and brain research will be discussed, along with the potential for nutrition to play a protective role in preserving better brain health in ageing.

1. **The Ageing Brain**
	1. Physiology and pathophysiology

The structure and metabolic pathways within the brain are progressively altered with ageing, though the precise aetiologies of ageing have not been fully elucidated. As people age, there is a reduction in brain volume in both grey and white matter(13), while white matter lesions increase(14) and there is development of amyloid plaques, neurofibrillary tangles, Lewy bodies, synaptic dystrophy and neuron loss(15,16), which have been suggested to parallel the progression of cognitive decline (17). There are also changes in the production of neurotransmitters – in particular serotonin and dopamine – which have been reported to decline by up to 10% per decade from early adulthood(14). Additionally, there is an increase in oxidative stress response(18) and more dysfunction of the blood brain barrier(19).

Normal ageing is associated with a decline in cognitive function, with most cognitive change observed in memory during the ageing process. MCI is a recognised clinical condition where individuals have evidence of cognitive impairment but do not meet the criteria for the diagnosis of dementia(20). Alzheimer’s disease (AD) is the most common form of dementia, accounting for 62% of cases, with other forms including vascular dementia, mixed, Lewy body and frontotemporal dementia(21). Depression in older adults is often referred to as ‘late–life depression’ and is reported more commonly in females than males(22-24). The depressive symptoms of older adults are thought to be different from those experienced by younger adults, as somatic and psychological symptoms are often accompanied by fatigue, hopelessness about the future, loss of appetite and sleep disturbance(22).

* 1. Pharmaceutical treatments

Pharmacological treatment for dementia is prescribed by specialist clinicians(25), but only a limited number of medications that target the biochemical abnormalities of neuronal loss are included within the National Institute for Health and Care Excellence (NICE) recommendations for dementia interventions. These include acetylcholinesterase (AChE) inhibitors (donepezil, galantamine, rivastigmine) and memantine (N-methyl-D-aspartate receptor antagonists). There are however a variety of pharmacological treatment options available for depression including tricyclic antidepressants, selective serotonin reuptake inhibitors, serotonin and noradrenaline reuptake inhibitors and selective noradrenaline reuptake inhibitors(26,27). Overall, poor response rates to these costly pharmacological treatments for depression have been observed(28,29), and despite significant investigation into the role of pharmacological treatments for dementia, no licenced medication can cure these diseases of the brain. Therefore, much efforts are currently focusing on options for prevention rather than treatment of brain disorders.

1. **Assessment of Brain Function**

The assessment of brain function for neurodegenerative diseases and depressive disorders in ageing is a developing area. There are numerous neurological tests available which are designed to assess and distinguish different individuals in their response to day-to-day cognitive tasks(30) and for the detection of common mental health disorders(31)*.* NICE has provided guidance on the recommended diagnostic criteria for depression(32) and dementia(33). For dementia, the guidelines emphasise the need to assess the following domains; attention and concentration, orientation, short- and long-term memory praxis, language and executive function. Furthermore, NICE recommends that formal tests should be conducted, including the Mini Mental State Examination (MMSE), 6-Item Cognitive Impairment Test (6-CIT), General Practitioner Assessment of Cognition (GPCOG) and 7-Minute Screen and that other factors known to influence performance such as education level, should also be taken into account. Lastly, only healthcare professionals with expertise in differential diagnosis and using international standardised criteria (such as the National Institute of Neurological Communicative Disorders) should be responsible for diagnosing subtypes of dementia(33).

Investigating cognitive and mental health outcomes via questionnaire-based assessments is the most common approach for assessing the effects of nutrition(34). For assessing brain health and function in relation to nutritional factors, studies should be aimed at prevention rather than treatment, and non-nutrition factors contributing to cognitive impairment and depression should be incorporated into studies and considered at the time of analysis(35). Concerning the specific tests to assess cognitive function, these should be carefully selected and should be based on a known or hypothesized relationship of a specific food/nutrient with cognitive function and not solely on their availability or ease of administration. It is also important that the tests are suitable for repeated administration, are appropriate to the population being studied, and are relatively simple to interpret and administer. More work is required using standardised tests across laboratories so that the speciﬁc tests or markers that are most sensitive to the nutrients tested can be established(30,35). Lastly, computerised cognitive assessments have been utilised and these should be considered for use in future trials in terms of their accuracy and ability to capture reaction-time data, standardisation of administration, availability of parallel versions of tasks for testing at multiple time-points, and availability in multiple languages(35)

1. **Food, Nutrition and Brain Health in Ageing**
2. Foods and dietary patterns

Increasing evidence implicates certain dietary patterns such as higher intake of fruits and vegetables(36) and fish(37) as being beneficial to brain health. The Mediterranean diet is receiving significant attention as regards its role in preserving cognitive health and protecting against depression in ageing. This diet is typically characterised by higher intakes of fruit, vegetables, wholegrains, fish, unsaturated fatty acids and a regular but moderate consumption of alcohol. A recent meta-analysis (*n* 34,168) showed that the highest Mediterranean diet score was associated with reduced incidence of developing cognitive disorders (RR 0.79 95% CI 0.70, 0.90)(38) while supplementation of the Mediterranean diet with olive oil or nuts was associated with improved cognitive function(39). Of note, studies using Magnetic Resonance Imaging (MRI) have shown that adherence to the Mediterranean diet was associated with larger cortical thickness (which in turn is associated with a lower risk of cognitive impairment)(40). There is also accumulating evidence to support a potential role for the Mediterranean diet in preventing depression in older adults, with cross-sectional and prospective studies showing inverse associations between Mediterranean diet score and risk of depression(41-45). Further well-designed intervention studies are however required to more fully investigate the potential role of the Mediterranean diet as a means of helping to preserve better brain health in ageing.

1. Specific Nutrients

*Protein and carbohydrates*

The role of dietary protein intake on cognitive function or mental health has not been extensively studied in ageing populations. Lower verbal memory scores were however observed in older people with lower dietary protein intakes(46). Additionally, higher dietary protein intake was found to be positively correlated with nonverbal learning, verbal memory and reduced risk of mild cognitive impairment or dementia(47,48). One randomised controlled trial (RCT) investigating the effects of dietary protein from red meat on cognitive function in older adults is in progress (ACTRN12613001153707) with results expected in 2018(49).

The association between carbohydrates and cognitive function is unclear because available evidence is scarce, with one Cochrane review identifying only one relevant RCT in older adults (50,51). However, higher dietary carbohydrate and sugar intakes were associated with lower cortical thickness, which is in turn associated with high risk of late life mild cognitive impairment and dementia(40). Whilst more research has focused on carbohydrates and depression, the available evidence is somewhat conflicting. One study of community dwelling older adults found that those with depressive symptoms consumed a diet with a higher glycaemic index (GI) and glycaemic load (GL)(52). A prospective investigation also reported that a high GI diet was associated with an increased risk of depression(53). Contrary to these findings, however, institutionalised older adults with depression were reported to consume diets with a lower GL(54). Given the inconsistencies in this area, there is clearly a need for further well-designed studies.

*Omega 3 fatty acids*

The fatty acid composition of the brain membrane is directly affected by diet and this has focused attention on the role of dietary fatty acids in brain health. There is evidence that long-chain *n*-3 polyunsaturated fatty acids (PUFA), eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), have potential benefits in cognitive and mental health(55,56). One meta-analysis of 10 RCT studies concluded that *n*-3 fatty acids may have a protective effect on certain cognitive domains in cognitively impaired patients, however, no effects were seen in healthy people or in AD sufferers(57). A recent Cochrane review, which identified three RCTs for inclusion involving 632 patients with mild to moderate AD, concluded that there was no convincing evidence that PUFA had a role in the treatment of people with existing dementia(58).

On the other hand, systematic reviews and meta-analyses of RCTs have reported significant clinical benefits of *n*-3 PUFA intervention in the treatment of depression. The use of predominantly EPA compared with DHA supplementation appears to have greater efficacy(59,60). Furthermore, supplementation with EPA-predominant formulas as an adjuvant therapy to antidepressants was found to have greater clinical efficacy in the treatment of depression (compared to antidepressants alone), but did not prevent depressive symptoms among populations without a diagnosis of depression(59,60). A Cochrane review in this area reported a small to modest non-clinical beneficial effect of *n*-3 PUFA in depression symptomology, but concluded that there was not enough good quality evidence to determine the effect on depression(61).

*Polyphenols*

The role of these phytochemicals in brain health and ageing is an emerging area(62-64). Large prospective studies have identified associations between the dietary intakes of total or specific polyphenols and cognitive function after up to 13 years of follow-up investigation(65-67). Supplementation with cocoa flavanol for periods of up to 2 months was reported to improve cognitive performance in a group of cognitively intact older adults(68). Of note, Brickman and colleagues(64) conducted a 3-month intervention and showed significant increases in cerebral blood volume in the dentate gyrus as measured by functional MRI (fMRI) in subjects who were assigned to a high flavanol treatment. Research into the role of polyphenols in depression in humans has been limited(69), though animal studies show promise in demonstrating antidepressant-like effects of polyphenols in mouse models(70).

*Vitamins*

Specific vitamins have been investigated in relation to brain health and disease. Oxidative stress is thought to be a major contributor to neurodegeneration and depression(18), thus antioxidants have received much interest. The roles of vitamin C(71-74), β-carotene(75-77) and vitamin E(78-81) have been explored, but no clear conclusions can be made and further work in the form of intervention studies is warranted. The postulated roles of vitamin D and B-vitamins have been more fully investigated in relation to their effects on brain health in ageing.

Following the discovery of the vitamin D receptor in the brain(82), evidence for the role of vitamin D in brain health has been accumulating. Systematic reviews and meta-analyses have shown that AD sufferers have lower serum vitamin D status than healthy controls, and that low serum vitamin D status is associated with worse cognitive outcomes(83-85). Recent longitudinal studies with mean follow-up periods of over 4 years found that lower vitamin D status was also associated with declining MMSE scores and accelerated cognitive decline(86,87). Furthermore, Hooshmand *et al*. used MRI to demonstrate that higher vitamin D status was associated with greater brain volumes(88), which is generally regarded as a valid marker of disease state and progression. Research investigating the role of vitamin D in depression is much less clear. Large cross-sectional and prospective studies reported that lower serum vitamin D status was associated with an increased risk of depression(89,90). One detailed systematic review, which included cross sectional, prospective and RCT data, concluded that lower vitamin D status may be a risk factor for late life depression(91).

c) One-carbon metabolism and related B-vitamins

Historically, B-vitamin deficiencies, in particular folate(92,93) and vitamin B12(94,95), and to a much lesser extent vitamin B6(96), have been linked with poorer psychiatric wellbeing. These B-vitamins play crucial roles in one-carbon metabolic pathways where they act as co-factors in DNA synthesis and repair, amino acid metabolism and methylation reactions, including the remethylation of homocysteine to methionine and subsequent generation of S-adenosylmethionine (SAM). SAM, the universal methyl donor, is involved in the methylation of DNA, phospholipids, proteins and neurotransmitters, thus reduced status of one or more of the B-vitamins involved in one-carbon metabolism may impair methylation processes(97,98). The inhibition of methylation reactions may in turn influence cognitive impairment in ageing in various ways(99), by perturbing the regulation of gene expression in the Beta amyloid pathway, by reducing the activity of protein phosphatase-2A or by impairing the formation of phosphatidylcholine enriched omega-3 fatty acids(99). Additionally, reduced tissue concentration of SAM may be linked to depression through perturbing monoamine (serotonin, dopamine and noradrenaline) synthesis and methylation(98). Apart from folate, vitamins B12 and vitamin B6, which have well-recognised roles in these pathways, riboflavin (in its co-factor forms flavin adenine dinucleotide, FAD and flavin mononucleotide, FMN) is also essential in one-carbon metabolism but its potential role in influencing brain health has rarely been considered.

Numerous observational studies have shown that lower status of folate, vitamin B12 and vitamin B6 (and/or higher concentrations of homocysteine; Hcy) are associated with cognitive deficit in ageing as extensively reviewed elsewhere(99,100). RCTs in older adults that include intervention with high-dose folic acid, vitamin B12 and vitamin B6 over 2 years or more have shown, not only improved cognitive performance(101-104), but also a reduced rate of brain atrophy in studies which have incorporated MRI(103,104). Notably the greatest slowing in atrophy (53%) was seen among participants with MCI and the highest Hcy concentrations at baseline (>13µmol/L), while cognitive function was preserved in those supplemented with B-vitamins and with a baseline Hcy concentration >11.3 µmol/L(102). The RCT evidence is not entirely consistent, however, as one recent and rather controversial meta-analysis in this area concluded that neither folic acid nor vitamin B12 had a beneficial effect on cognition in older adults(105). This paper was however widely criticised at the time of publication, mainly as a result of the inclusion criteria used to select the trials for investigation, and thus the findings are in general not widely accepted by experts in this area(106,107). It is clear that further appropriately designed RCTs are needed, especially those targeting participants with low B-vitamin status (and in those at most risk of cognitive decline) as they are likely to benefit the most from optimising B-vitamin concentrations to achieve better cognitive health in ageing. Furthermore, research investigating the protective role of riboflavin on cognitive function is greatly lacking, albeit some evidence from older studies investigating riboflavin showed that lower biomarker status was associated with cognitive impairment(108). Clearly there is a need for riboflavin to be considered in future RCTs.

The role of B-vitamins in depressive disorders has not received as much interest as studies of cognitive disorders, although some observational (**Table 1)** and intervention **(Table 2)** evidence exists. A meta-analysis of 19 observational studies concluded that low folate status was associated with a significantly greater risk of depression(109). Low dietary intakes(110,111) or biomarker status(112-115) of vitamin B12 have also been linked with an increased risk of developing depression. Only a limited number of studies have considered the role of vitamin B6, but available evidence suggests an inverse association between vitamin B6 biomarker status (plasma pyridoxal 5'-phosphate) and depression(111,116,117). Far less evidence exists in relation to riboflavin, although one early study reported lower biomarker status of riboflavin in psychiatric inpatients(96). A number of RCTs have considered the role of B-vitamin supplementation alone(118-121) or as an adjunct to anti-depressant medications(122,123). The results are somewhat conflicting, however, and no clear conclusions have emerged, partly because of major methodological differences among studies. Reviews of the available evidence in relation to depression have concluded that folate and vitamin B12 may have roles in the longer-term management of this condition(124,125).

Overall, there is considerable evidence to suggest that folate, vitamin B12 and vitamin B6 have protective effects on cognitive function, and potentially against depressive symptoms in ageing, however further RCTs of appropriate duration in suitable populations, and ideally interventions combining all four relevant B-vitamins, are required to support these findings.

1. **Use of Novel Imaging Technologies in Nutrition and Brain Research**

Following the 2009 Nutrition and Mental Performance Task Force of the European Branch of the International Life Sciences Institute (ILSI Europe) workshop, a recommendation was developed suggesting the inclusion of brain imaging biomarkers as secondary endpoints to clinical and cognitive measures(35). Brain imaging techniques have been increasingly utilised in recent years and provide an objective and highly robust means of assessing brain structure, function and response to nutrition, with advantages and disadvantages associated with each of their use, as reviewed in detail elsewhere(126) (**Table 3)**. Electroencephalography (EEG) and magnetoencephalography (MEG) are two similar techniques for functional brain imaging and have the highest temporal resolution compared to other imaging techniques.

In recent years, some of these brain-imaging techniques have been utilised to advance nutrition research in ageing. One notable study referred to earlier in this review(103) effectively used MRI and confirmed the beneficial effects of B-vitamins on cognition shown previously in older adults with MCI, in particular in those with good status of PUFA(127). Additionally, Brickman used fMRI and demonstrated higher brain activation in specific regions of the brain in participants who consumed high dose cocoa flavanols(64). In a study of 239 older adults, diffusion tensor imaging (which in some cases has been suggested to be a better predictor of cognitive decline than other biomarkers)(128), identified better white matter integrity in those who consumed more *n-*3 and *n-*6 PUFAs and vitamin E(129). EEG has also been used, with one recent report showing improved memory and functional connectivity in the delta band in response to Souvaid®, a nutritional supplement containing PUFAs uridine, choline, phospholipids, folic acid, vitamin B6, B12, C, E and selenium in mild Alzheimer type patients(130). Positron Emission Tomography Imaging (PET) has also been conducted within a 3-week intervention study, albeit in a very small study of only 11 women, leading to the conclusion that omega 3 supplementation did not affect brain glucose metabolism in healthy older people(131).

It is clear that imaging techniques provide an objective means to improve the evidence base in this area, in particular in relation to proposed mechanisms. At this time, however, the number of studies utilising brain-imaging techniques to investigate the role of diet in brain health in ageing are limited. MEG has been approved by the US Food and Drug Administration (FDA) for use within clinical and research settings as a means to assess and investigate cognitive dysfunction(132), AD(133,134) and depression(135). However, to our knowledge, no work has been published using MEG for nutrition studies in older adults. The application of these new technologies in the field of nutrition, in combination with clinical and questionnaire-based assessments, could provide much potential for robust investigation in future studies, furthering knowledge and discovery.

**Conclusions and Public Health Implications**

Nutrition has important roles in preserving cognition and reducing the risk of late life depression. Emerging evidence in this area implicates subclinical deficiencies of certain nutrients in cognitive decline and depression in older adults. Future studies should address the gaps in the literature, in particular in identifying of the threshold for optimal nutrient levels required to prevent or delay declining brain health. At this time, the evidence for potential protective effects is strongest in relation to B-vitamins, *n*-3 PUFAs and polyphenols. If confirmed, a public health strategy to improve status of these key nutrients may help to achieve better cognitive and mental health and thus improve quality of life in older age. Future well-designed RCTs (ideally incorporating imaging techniques such as MEG) may provide a more robust basis for confirming effective nutrition interventions, which if implemented could reduce the risk of cognitive and mental health disorders in ageing and the related burden on health services and society overall.

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**Table 1. Summary of observational studies investigating the association of B-vitamin intake and status with depression in older adults**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Author** | **Country** | **Study Design** | ***n*** | **Assessment** | **B-vitamin Measurement** | **Outcome** |
| Gougeon *et al* 2016(136)  | Quebec, Canada | Longitudinal | 1368 | GDS/ anti-depressants usage | 3x 24 h-recalls | Decreased depression risk among women with higher intakes of vitamin B6. |
| Moorthy *et al* 2012(137) | Boston, USA | Cross sectional | 1955 | MMSECES-D | Plasma folate, vitamin B12, B6 tHcy | Low B12 concentration associated with higher depression scores. |
| Robinson *et al* 2011(112) | Dublin, Ireland | Cross sectional | 252 | CES-D | Serum folate, B12, Holo TC | Total B12 and Holo TC concentrations inversely associated with depressive symptoms. |
| Beydoun *et al* 2010(138)  | USA | Cross sectional | 2524 | PHQ | Serum folate, B12, tHcy | Inverse association between folate concentrations and depressive symptoms; dose response relationship. |
| Skarupski *et al* 2010(139)  | Chicago,USA | Longitudinal | 3503 | CES-D | Semi quantitative FFQ | High dietary intakes of B6 and B12 protective against depressive symptoms. |
| Ng *et al* 2009(140)  | Singapore | Cross sectional | 669 | GDS | Serum folate, B12, tHcy | Lower concentrations of folate or deficient B12status associated with greater risk of depression. |
| Sanchez-Villegas *et al* 2009(110) | Boston,USA | Observational | 9670 | Self-reported depression, anti-depressants usage | Semi quantitative FFQ | Low dietary folate intake associated with depression among men; low B12 intake associated with depression in women; no associations with vitamin B6 intake. |
| Murakami *et al* 2008(141)  | Japan | Cross sectional | 517 | CES-D | Diet history questionnaire | Dietary folate inversely associated with depressive symptoms in men. No clear association for other B vitamins. |
| Kim *et al* 2008(142)  | Korea | Cross sectional & prospective | 732 | Geriatric Mental State | Serum folate, B12 tHcy | Lower baseline B12 concentrations associated with depression. Lower folate concentrations at baseline associated with higher risk of depression 2 years later.  |
| Dimopoulos *et al* 2007(143) | Greece | Observational | 66 | GDS | Plasma Folate, B12, tHcy, | Lower folate and vitamin B12 or higher tHcy concentrations correlated with depressive symptoms. |
| Ramos *et al* 2004(144)  | California, USA | Observational | 1510 | CES-D | Plasma folate, B12, tHcy | Participants in lowest tertile of plasma folate at increased risk of depression. |
| Bjelland *et al* 2003(145)  | Norway | Observational | 5948 | HADS | Serum folate,B12, tHcy | Elevated tHcy significantly related to depression. |
| Tiemeier *et al* 2002(146) | Netherlands | Observational | 3384 | CES-D | Serum folate, B12, tHcy | Depressive disorder more likely with vitamin B12 deficiency.  |

Abbreviations: CES-D, Centre for Epidemiological Studies Depression Scale; GDS, Geriatric Depression Scale; HADS, Hospital Anxiety and Depression Scale; MMSE, Mini Mental State Examination; PHQ, Patient Health Questionnaire; tHcy, total plasma homocysteine.

**Table 2. Summary of RCTs investigating the effect of B-vitamin supplementation on depression in older adults**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Study** | **Area** | **Cohort** | **Intervention** | **Duration** | **Outcome** |
| *B-vitamin intervention alone* |  |  |
| Okereke et al 2015(120) | USA | *n* 433163.6 years | FA: 2.5mg, B12: 1mg, B6: 50mg or Placebo | 7 years | No effect on depression outcomes in participants without prior depression. |
| Walker et al 2010(118) | Australia | *n* 90965 years | FA:0.4mg, B12: 0.1mg or Placebo | 2 years | FA plus B12 was not effective in reducing depressive symptoms in participants with elevated psychological distress. |
| Almeida et al 2010(119) | Australia | *n* 27363 years | FA: 2mg, B12: 0.5mg, B6: 25mg or Placebo | 6.9-7.2 years | Reduction in risk of major depression, in participants with no previous major depressive episodes. |
| Ford *et al* 2008(121) | Australia | *n* 299≥75 Years | FA: 2mg, B12: 0.4 mg, B6: 25 mg or Placebo | 2 years | No effect on depressive symptoms or development of depression in participants without a prior diagnosis of depression. |
| *B-vitamin supplement as adjunct to anti-depressant medications* |  |  |
| Almeida et al 2014(123) | Australia | *n* 15350+ years | 20-40g Citalopram with FA: 2mg, B12: 0.5mg, B6; 25mg or placebo | 52 weeks | B vitamins did not increase 12-week efficacy ofantidepressants, but enhanced and sustained antidepressant response over 1 year in participants with depression. |
| Coppen and Bailey 2000(122) | UK | *n* 12741.9 : 44.3 years | 20 mg fluoxetine withFA: 500 mg or placebo | 10 weeks | FA significantly improved the action of fluoxetine in participants with depression. |

Abbreviations: FA, Folic acid.

**Table 3. Brain Imagining techniques for use in nutrition research**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Technique** | **Measurement method** | **Information obtained** | **Advantages** | **Disadvantages** |
| Computerized Tomography (CT) | X-rays | Structural images of the brain | Quick, relatively inexpensive, less stringent requirement for patients.  | Exposure to radiation  |
| Magnetic Resonance Imaging (MRI) | Magnetic fields and radiofrequency pulses | Detailed structural images of brain tissue (white and grey matter, blood vessels and bone) | Safe, non-invasive, good availability, repeatable  | Unsuitable if participants have ferromagnetic implants or claustrophobia, costly to conduct |
| Diffusion Tensor Imaging (DTI) | MRI-based technique using thermally induced self-diffusion of water as a probe | Mapping of the microstructures in the white and grey matter | Visualisation of microstructures, safe, non-invasive, good availability, repeatable | Unsuitable if participants have ferromagnetic implants or claustrophobia, costly to conduct |
| Functional MRI (fMRI) | MRI-based technique using blood oxygen level dependant imaging | Visualisation of changes in blood flow, identification of areas of increased cerebral blood volume | Safe, non-invasive, good availability, repeatable | Unsuitable if participants have ferromagnetic implants or claustrophobia, costly to conduct |
| Positron Emission Tomography Imaging (PET) | Radioactively labelled tracers once they begin to decay; the two gamma rays released are detected by the scanners | Measurement of the metabolic and physiological processes of the brain | Provide measures of regional cerebral metabolism, blood flow and neurotransmitter metabolism  | Low availability requires intravenous injection, use of radioactive compounds, limited use in diabetic participants |
| Single-Photon Emission Computerised Tomography Imaging (SPECT) | Similar principles to the PET, however the radioactively labelled tracers used emit a single gamma ray | Neurotransmitter distribution and blood perfusion | Provide measures of regional cerebral metabolism, blood flow and neurotransmitter metabolism  | Low availability requires intravenous injection, use of radioactive compounds, limited use in diabetic participants |
| Electroencephalography (EEG) | Electrodes with conductive media are used to detect electric signals | Ionic currents that flow during synaptic excitation in the apical dendrites of pyramidal cells in the cerebral cortex | Relatively inexpensive, non-invasive, good temporal resolution, widely available  | Poor spatial resolution, preparation timely |
| Magnetoencephalography (MEG) | Specialised detectors superconducting quantum interference devices are used to record the magnetic signals | Ionic currents that flow during synaptic excitation in the apical dendrites of pyramidal cells in the cerebral cortex | Non-invasive, highest temporal and spatial resolution. | Limited availability, costly, ferromagnetic implants may interfere with scan |