Current evidence linking nutrition with brain health in ageing

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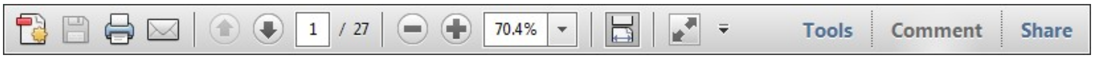
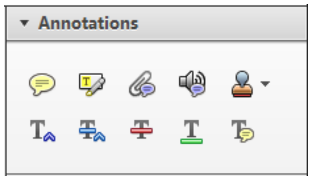


This will open up a panel down the right side of the document. The majority of tools you will use for annotating your proof will be in the Annotations section, pictured opposite. We've picked out some of these tools below:

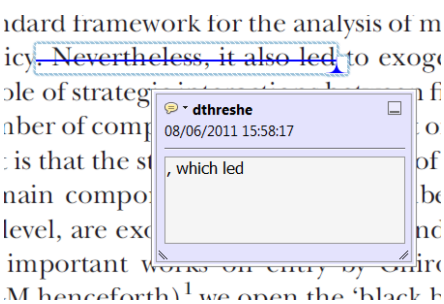


1. Replace (Ins) Tool – for replacing text.

Strikes a line through text and opens up a text box where replacement text can be entered.

How to use it

- Highlight a word or sentence.
- Click on the Replace (Ins) icon in the Annotations section.
- Type the replacement text into the blue box that appears.

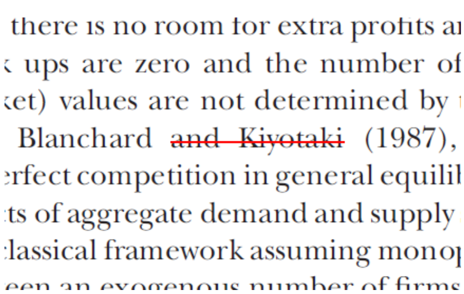


2. Strikethrough (Del) Tool – for deleting text.

Strikes a red line through text that is to be deleted.

How to use it

- Highlight a word or sentence.
- Click on the Strikethrough (Del) icon in the Annotations section.

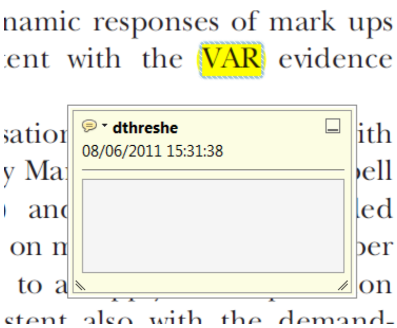


3. Add note to text Tool – for highlighting a section to be changed to bold or italic.

Highlights text in yellow and opens up a text box where comments can be entered.

How to use it

- Highlight the relevant section of text.
- Click on the Add note to text icon in the Annotations section.
- Type instruction on what should be changed regarding the text into the yellow box that appears.

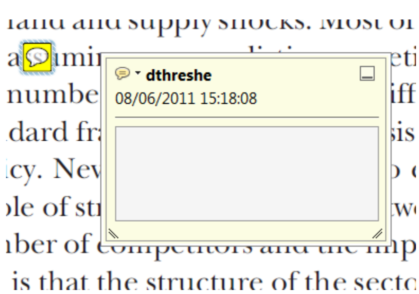


4. Add sticky note Tool – for making notes at specific points in the text.

Marks a point in the proof where a comment needs to be highlighted.

How to use it

- Click on the Add sticky note icon in the Annotations section.
- Click at the point in the proof where the comment should be inserted.
- Type the comment into the yellow box that appears.

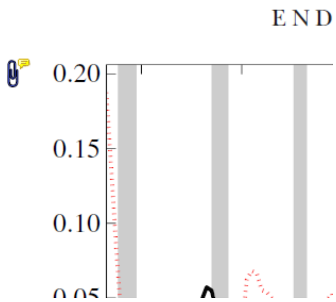


5. Attach File Tool – for inserting large amounts of text or replacement figures.

Inserts an icon linking to the attached file in the appropriate place in the text.

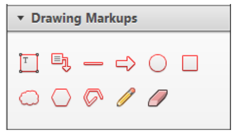
How to use it

- Click on the Attach File icon in the Annotations section.
- Click on the proof to where you'd like the attached file to be linked.
- Select the file to be attached from your computer or network.
- Select the colour and type of icon that will appear in the proof. Click OK.



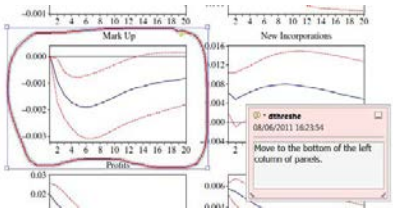
6. Drawing Markups Tools – for drawing shapes, lines and freeform annotations on proofs and commenting on these marks.

Allows shapes, lines and freeform annotations to be drawn on proofs and for comment to be made on these marks.



How to use it

- Click on one of the shapes in the Drawing Markups section.
- Click on the proof at the relevant point and draw the selected shape with the cursor.
- To add a comment to the drawn shape, move the cursor over the shape until an arrowhead appears.
- Double click on the shape and type any text in the red box that appears.



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Current evidence linking nutrition with brain health in ageing

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Abstract

Cognitive dysfunction and depression are significant problems of ageing with major health and socio-economic impacts; therefore, preventing or delaying the onset of these disorders should be a public health priority. In particular, there is a need to identify modifiable factors that could be targeted to promote better brain health in ageing. Epidemiological studies indicate a protective role for certain dietary patterns, in particular the Mediterranean diet, and for specific nutrients, including *n*-3 polyunsaturated fatty acids, polyphenols and B vitamins. ~~However,~~ the evidence to date from randomised controlled trials is generally inconsistent, ~~although~~ there is clearer evidence to support a role for folate and related B vitamins in slowing the progression of cognitive decline and possibly reducing the risk of depression in ageing. Future studies incorporating new technologies offer much promise for the development of effective nutrition strategies that could reduce the risk of cognitive and mental disorders and improve quality of life in our ageing population.

Keywords: ageing, B vitamins, cognitive function, depression, fatty acids, nutrition

Introduction

The global population is ageing with the number of those aged 60 years and over predicted to reach two billion by 2050 (United Nations Department of Economic and Social Affairs/Population Division 2009). An estimated 46.8 million people are living with dementia worldwide, and this figure is predicted to double in the next 20 years, with associated costs to the global economy currently estimated at over $818 billion/year (Prince *et al.* 2015). Depression is a leading cause of disability, currently costing approximately £7.5 billion annually in England alone, and projected to increase by 67% by 2026 (National Collaborating Centre for Mental Health 2010). Given the significant impact of these conditions, there is a need to identify modifiable factors that could be targeted to promote better brain health in 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 (Panza *et al.* 2008; Rechenberg 2016).

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The ageing brain

Ageing affects the brain from a cellular to a functional level. The brain has a high metabolic rate; therefore, oxidative stress and inflammation are common in ageing neural tissue (Bishop *et al.* 2010). On average, brain size decreases with age in later life and although there is no loss of cortical volume, there is white matter atrophy (Silverman *et al.* 1997). The rate of this atrophy is known to be a marker of cognitive decline (Fox *et al.* 1999) and white matter lesions in ageing are linked with late onset depression (Wang *et al.* 2014). Neurodegeneration is the loss of neuronal processes and nerve cells. This can lead to neurodegenerative disorders which are characterised by selective loss of neurons in the motor, sensory and cognitive systems. This affects memory, cognition, language, personality and mood and can have sporadic and/or hereditary origins (Gelb 2016).

Mild cognitive impairment can be described as a rate of cognitive decline greater than expected for an individual's age and education level but that does not interfere notably with activities of daily life (Gauthier *et al.* 2006). Of note, however, is that an estimated 50% of those with mild cognitive impairment will go on to develop dementia within 5 years (Gauthier *et al.* 2006). Dementia is characterised by progressive deterioration of multiple cognitive domains leading to impaired daily functioning, with Alzheimer's disease being the most common cause of dementia in older adults (Prince *et al.* 2014). The World Health Organisation (2014) defines mental health as a state of 'complete physical, mental and social wellbeing and not merely the absence of disease or infirmity'; mental illness includes depression and anxiety as common disorders. A number of modifiable risk factors for declining cognitive and mental health have been identified, including dietary patterns and specific nutrients (Smith 2008; Stahl *et al.* 2014; Gallagher *et al.* 2016; Kennedy 2016; Rechenberg 2016). Ageing itself is associated with a reduction in the quantity of food consumed, altered metabolism and decreased absorption of nutrients, all of which can increase the risk of malnutrition (Wakimoto & Block 2001). Therefore, nutritional approaches to prevent or slow the progression of cognitive decline are of much current research interest.

Foods and brain health

Increasing evidence implicates certain dietary patterns, such as high intake of fruit and vegetables (Kang *et al.* 2005) and fish consumption (Barberger-Gateau *et al.* 2007), as being beneficial to brain health. Compliance with a Mediterranean diet (typically characterised by higher intakes of fruit, vegetables, wholegrains, olive oil and fish) has been associated with lower risk of Alzheimer's disease and slower progression of symptoms from mild cognitive impairment to Alzheimer's disease (Scarmeas *et al.* 2006; Solfrizzi *et al.* 2010; Singh *et al.* 2014). Adherence to a Mediterranean diet also has been associated with a protective effect against depression (Psaltopoulou *et al.* 2013). These findings were recently confirmed in a study of 4470 participants, aged from 45 to 79 years, which found significantly lower depression scores in those with greater adherence to a Mediterranean diet (Veronese *et al.* 2016). Although there is some biological basis for the protective role of the Mediterranean diet in brain health, the findings do not prove causality as the studies to date have predominantly been observational.

Specific nutrients and brain health

Fatty acids

The fatty acid composition of brain membrane is directly affected by ~~the~~ 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, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) have potential benefits in cognitive and mental health. The suggested mechanism for the effects of these fatty acids is via their antithrombotic and anti-inflammatory properties (Gillette-Guyonnet *et al.* 2013) and their potential interactions with neurotransmitters via phospholipid metabolism and regulation of signal transduction (Grosso *et al.* 2014a). Regular consumption of dietary *n*-3 polyunsaturated fatty acids has been associated with reduced risk of cognitive decline and reduced development of incident dementia in epidemiological studies (Jicha & Markesbery 2010). Likewise, higher dietary DHA has been associated with lower incidence of dementia (Schaefer *et al.* 2006; Lopez *et al.* 2011). Randomised controlled trials (RCTs) of *n*-3 polyunsaturated fatty acid supplementation have, however, shown somewhat inconsistent results with regard to cognitive function (Freund-Levi *et al.* 2006; Quinn *et al.* 2010; Yurko-Mauro *et al.* 2010). Furthermore, the relationship between fatty acids and cognitive outcomes is complex since higher intakes of *n*-6 fatty acids, irrespective of *n*-3 polyunsaturated fatty acid intake, seem to negate any of the aforementioned beneficial effects of *n*-3 polyunsaturated fatty acids (Jicha & Markesbery 2010). One meta-analysis of RCTs intervening with supplemental *n*-3 polyunsaturated fatty acids concluded that the beneficial effects on brain health may be confined only to patients with mild cognitive impairment (Mazereeuw *et al.* 2012); however, this interpretation requires further investigation.

In two recent meta-analysis of RCTs, EPA supplementation was found to benefit patients with a diagnosis of depression; however, in those with nonclinical depression, the findings were far less clear

(Grosso *et al.* 2014b; Hallahan *et al.* 2016). A recent Cochrane review concluded that there was insufficient evidence to support increased *n*-3 polyunsaturated fatty acid intake as a treatment for depression, highlighting the need for further investigation in this area (Appleton *et al.* 2015).

Protein and carbohydrates

The role of dietary protein in cognitive function and 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 (Goodwin *et al.* 1983). Additionally higher dietary protein intake was found to be positively correlated with non-verbal learning and verbal memory (Koehler *et al.* 1997) and reduced risk of mild cognitive impairment or dementia (Roberts *et al.* 2012). One RCT investigating the effects of dietary protein from red meat on cognitive function in older adults is ongoing (Daly *et al.* 2015).

The association between carbohydrates and cognitive function is unclear because available evidence is scarce (Power *et al.* 2015), with a Cochrane review identifying only one RCT in older adults (Ooi *et al.* 2011). While 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 had a diet with a higher glycaemic index (GI) and glycaemic load (GL) (Mwamburi *et al.* 2011). A prospective investigation also reported that a high GI diet was associated with an increased risk of depression (Gangwisch *et al.* 2015). Contrary to these findings, research in institutionalised older adults reported that those suffering from depression had diets with a lower GL (Aparicio *et al.* 2013). Given the inconsistencies within the evidence base in this area, there is clearly a need for further well-designed studies.

Polyphenols and vitamins

Inflammation is thought to be involved in the neurodegenerative cascade resulting in cognitive decline (Gorelick 2010), and evidence suggests a protective anti-inflammatory role for flavonoids against cognitive decline and Alzheimer's disease (Commenges *et al.* 2000; Letenneur *et al.* 2007; Schaffer *et al.* 2012). In one large prospective study of 5395 older adults in the Netherlands, polyphenol intake was associated with a reduced risk of dementia in smokers (Engelhart *et al.* 2002). Likewise, dietary polyphenol intake was also associated with cognitive performance in 2574 middle-aged French participants (Kesse-Guyot *et al.* 2012). Of greater note, new evidence from a recent RCT of healthy older adults reported that intervention with high doses of cocoa-flavanol enhanced dentate gyrus function, a brain area essential for learning and memory, which was measured by magnetic resonance imagining (MRI) and cognitive tests (Brickman *et al.* 2014). In the case of depression, animal studies have shown anti-depressant effects of numerous polyphenols, postulated to be related to their anti-inflammatory and neurotransmitter modulation roles (Pathak *et al.* 2013). Although positive effects of cocoa polyphenols on mood were reported in one small study of 87 middle-aged participants (Pase *et al.* 2013), the evidence from human studies is generally scarce and expert groups have called for further co-ordinated research in this area (Ward & Pasinetti 2016).

Oxidative stress is thought to be a major contributor to neurodegeneration and depression; thus, antioxidants have received particular attention in the study of older adults. Although large prospective studies have failed to demonstrate a protective effect of either dietary or supplemental ascorbic acid on cognitive function in older adults (Luchsinger *et al.* 2003; Laurin *et al.* 2004; Devore *et al.* 2010), the studies had significant limitations including the lack of a biomarker measure of vitamin C status. With regard to mental health, an early RCT with an antioxidant supplement containing vitamins A, E and C in 205 participants reported substantial increases in plasma ascorbic acid concentrations and correspondingly better mood outcomes after one year (Smith *et al.* 1999). Likewise, more recent cross-sectional and prospective studies have reported lower dietary intakes or plasma concentrations of ascorbic acid among older adults with depression (Merrill *et al.* 2008; Hamer *et al.* 2011; Payne *et al.* 2012). More robust RCTs, which include both biomarker and dietary intake measures, are required to further explore the role of vitamin C in mental health.

There is extensive literature in the area of vitamin D and the ageing brain. Of note, a 7-year follow-up study of 498 women aged 75 years and older identified significantly lower risk of Alzheimer's disease for those participants in the highest quintile of dietary vitamin D intake at baseline (Annweiler *et al.* 2012). In a recent meta-analysis of observational studies, patients suffering from Alzheimer's disease were found to have significantly lower serum vitamin D concentrations compared with matched cognitively healthy controls (Annweiler *et al.* 2013). However, combined supplementation with vitamin D and calcium was not found to decrease the risk of dementia or cognitive decline in a RCT involving 4143 older women from the US (Rossom *et al.* 2012). In the case of depression, large cross-sectional ($n = 2598$) and prospective ($n = 2839$) studies have linked lower serum vitamin D status with an increased risk of depression (Williams *et al.* 2014; Brouwer-Brolsma *et al.* 2016). The available evidence from intervention studies, however, has not confirmed a causative relationship for vitamin D in relation to the risk of depression (Li *et al.* 2014; van den Berg *et al.* 2016).

B vitamins and cognition in ageing

The role of folate and related B vitamins in brain health in ageing, and related mechanisms involving one-carbon metabolism, is an area of active research worldwide. Within one-carbon metabolism, folate, along with vitamins B_{12} and B_6, and riboflavin are cofactors in DNA synthesis and repair, amino acid metabolism and methylation reactions, including the remethylation of homocysteine to methionine and subsequent generation of S-adenosylmethionine. The latter metabolite is essential for neurotransmitter synthesis and thus vital for brain function and activity (McGarel *et al.* 2015).

A number of observational studies have shown that lower status of folate, vitamin B_{12} and vitamin B_6 (and/or higher concentrations of homocysteine) are associated with cognitive deficit in ageing (Smith & Refsum 2016). RCTs have addressed the hypothesis that optimising B vitamin status by supplementing with folate alone, or in combination with vitamins B_{12} and/or B_6, will delay cognitive decline in older adults. Available RCTs in older adults that include intervention with high-dose folic acid, vitamin B_{12} and vitamin B_6 over 2 years or more have shown not only improved cognitive performance (Durga *et al.* 2007; Smith *et al.* 2010; de Jager *et al.* 2012; Douaud *et al.* 2013) but, in those incorporating MRI, also a reduced rate of brain atrophy (Durga *et al.* 2007; Smith *et al.* 2010; de Jager *et al.* 2012; Douaud *et al.* 2013). The RCT evidence is not entirely conclusive, however, with one notable trial from New Zealand failing to observe a significant beneficial effect of folic acid, vitamin B_{12} and vitamin B_6 on cognition (McMahon *et al.* 2006), possibly owing to the inclusion of participants with generally high baseline folate status and thus unlikely to benefit from intervention aimed at improving status. One recent and rather controversial meta-analysis in this area concluded that neither folic acid nor vitamin B_{12} had a beneficial effect on cognition in older adults (Clarke *et al.* 2014). The article was 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 not generally accepted by the scientific community in this area (Garrard & Jacoby 2015; Smith *et al.* 2015). It is clear that further well-designed RCTs are needed, especially those targeting participants with low B vitamin status as they are likely to benefit the most from increasing B vitamin concentrations to achieve better cognitive health in ageing.

The role of B vitamins in depressive disorders has not received as much interest as in cognitive function. However, one meta-analysis of 19 observational studies reported a significant relationship between low folate status and risk of depression (Gilbody *et al.* 2007). Low dietary intake and status of vitamin B_{12} have also been linked with an increased risk of depression (Reynolds 2006; Kim *et al.* 2008; Ng *et al.* 2009; Sánchez-Villegas *et al.* 2009; Robinson *et al.* 2011; Moorthy *et al.* 2012). RCTs of B vitamin supplementation as an adjunct to anti-depressant medications (Coppen & Bailey 2000; Almeida *et al.* 2014) or alone (Almeida *et al.* 2010; Walker *et al.* 2010) have provided mixed results and no clear conclusions, partly because of major methodological differences among studies. Reviews of the available evidence linking B vitamins with depression have concluded that folate and vitamin B_{12} may have roles in the longer term management of this condition (Taylor *et al.* 2004; Almeida *et al.* 2015).

Use of novel technologies in nutrition and brain research

Validated questionnaire-based assessments are the most common means of investigating cognitive and mental health outcomes and indeed are most informative in regard to the effect of nutrition on behaviour (Macready *et al.* 2010). However, in order to study the role of nutrition in brain function, the emerging use of brain imaging techniques in recent years provides an objective and highly robust means of assessing brain function and response (de Jager & Kovatcheva 2010). A number of such techniques are available and have been reviewed in detail elsewhere (Sizonenko *et al.* 2013). Magnetic resonance imaging (MRI) is a structural imaging technique that provides detailed pictures of brain tissue (white and grey matter, blood vessels and bone) using magnetic fields and radiofrequency pulses. Functional MRI (fMRI) uses blood oxygen level-dependant imaging to visualise changes in blood flow, in order to identify areas of neural activity within the brain. Electroencephalography (EEG) and magnetoencephalography (MEG) are two techniques for functional brain imaging that record electric and magnetic activities of the brain at the scalp and have the highest temporal resolution compared to other imaging techniques.

In recent years, these imaging techniques have been utilised in nutrition research. One notable study, referred to earlier in this review, effectively used MRI to confirm the beneficial effects of B vitamins on cognition in older adults over a 2-year intervention period (Smith *et al.* 2010). Another study used fMRI to demonstrate higher brain activation in specific regions of the brain in participants who consumed a nutritionally balanced breakfast (Akitsuki *et al.* 2011). EEG has also been used to investigate the effects of diet on brain function, with one recent report showing improved memory and functional connectivity in the delta band in response to Souvenaid®, a nutritional supplement, in mild Alzheimer-type patients (Ritchie *et al.* 2014). In recent years, MEG has been approved by the US Food and Drug Administration (FDA) and is being used for clinical and research purposes, including investigating cognitive dysfunction, Alzheimer's disease and depression (Maestú *et al.* 2008; Cheng *et al.* 2012; de Haan *et al.* 2012; Kurita *et al.* 2016). The application of these new technologies in the field of nutrition, in combination with clinical and questionnaire-based assessments, provides much potential for robust investigation in future studies, furthering knowledge and discovery, in an effort to reduce the burden of declining brain health in ageing.

Conclusions

Undoubtedly, nutrition has an important role in preserving cognitive and mental health and thus improving quality of life in older age. The impact of specific nutritional factors on brain ~~health~~ in ageing is an area of active investigation worldwide. Emerging evidence implicates subclinical deficiencies of certain nutrients in cognitive decline and poor mental health in older adults; however, the threshold for nutrient levels to prevent or delay declining brain ~~health~~ is still unknown. If the findings of studies described in this review, which show promise in relation to B vitamins, *n*-3 polyunsaturated fatty acids and polyphenols, are confirmed, a public health strategy to improve status of these key nutrients may help to achieve better cognitive and mental health in ageing. Future studies incorporating imaging techniques offer a robust basis for confirming effective nutrition interventions that could reduce the risk of cognitive and mental decline in ageing and the related burden on health services.

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Conflicts of interest

The authors declare no conflict of interest.

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