



Conference on ‘Diet, nutrition and mental health and wellbeing’ Symposium 1: Nutrition and brain function: how strong is the evidence?

Nutrition research in cognitive impairment/dementia, with a focus on soya and folate

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Observational studies and treatment trials investigating nutrition and cognitive function, with a focus on folate and soya and dementia, were reviewed. Data suggested that effects of folic acid based interventions may only be shown before cognitive decline is evident and/or if people are folate deficient. In older people in Indonesia, Hawai'i and China, tofu, which can contain high levels of phytoestrogens, was found to increase dementia risk. This association was not mediated by a vegetarian diet, socioeconomic status, formaldehyde, thyroid function, or loss of teeth. On the other hand, human observational and animal treatment studies suggested that tempe, a fermented soya product containing phytoestrogens and folate, reduced dementia risk and improved memory. High oestrogen levels were found to increase dementia risk in older women. However, in women with adequate serum folate, high oestrogen levels did not confer additional dementia risk and may protect ageing neurons. In conclusion, reviews seem to suggest that folic acid interventions are only effective on cognitive outcomes in people who are folate deficient and do not have cognitive impairment. Frequent consumption of tofu may have detrimental effects on memory and increase dementia risk in older East Asian people, while tempe may reduce these risks. Possibly folate in tempe offsets the potential negative effects of oestrogenic compounds on ageing neurons.

Dementia: Soya: Folate: Memory: Phytoestrogen

Dementia is a global and growing problem with an ageing population worldwide⁽¹⁾. While dementia risk increases with age, it is not necessarily a consequence of this, making prevention of the syndrome possible. The most common form of dementia is Alzheimer's disease, characterised by distinct pathology in the brain, such as plaques mainly consisting of β -amyloid, and neurofibrillary tangles, which interfere with normal brain function. Clinically, Alzheimer's disease is characterised by a gradual and progressive decline in cognitive functions affecting daily and social activities⁽²⁾. However, at

post-mortem, when the cause of dementia is confirmed, presence of other pathologies (e.g. vascular, Lewy bodies) is often common⁽³⁾. Dementia costs are high, currently estimated at \$818 billion/year, increasing to \$1 trillion by 2018⁽¹⁾. These costs include formal and informal care provided by families and others. Currently 47 million people worldwide are estimated to be afflicted with dementia, which number will almost double by 2030 to 75 million and to 132 million by 2050⁽¹⁾. This growth in numbers of dementia cases is particularly high in developing countries, with a 300% increase in China and a

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100% increase in India and Indonesia. With possibly half of all dementia cases predicted to live in Asia by 2050, the present research on modifiable risk and protective factors was conducted in these parts, focusing in the present paper on consumption of soya containing phytoestrogen rich foods and dementia risk. Because folate has long been investigated as a potential protective agent which may also interact with (phyto)oestrogens, data for folic acid treatment to promote cognitive function and decrease dementia risk were also reviewed. These reviews are based on earlier systematic reviews^(4,5).

Risk factors for dementia: demographic and cardiovascular risk factors

As said, an important risk factor for dementia is increasing age⁽⁶⁾. Other non modifiable risk factors are being of the female gender and having had few years of education⁽⁶⁾. This may at least partly explain the increase in numbers of cases in developing countries over the past decades, as many previously poorly educated people are now reaching older age, due to better medical and health facilities, education and promotions. Other possible modifiable risk factors for dementia are shared with (cerebro- and cardio-) vascular disease, such as smoking, inactivity, diabetes mellitus, obesity, high blood pressure and high total cholesterol⁽⁷⁻⁹⁾. Each of these factors individually doubles the risk for dementia. As they can have cumulative effects, for instance, having high blood pressure, diabetes and high total cholesterol can increase the risk for dementia in later life by a factor 6⁽⁷⁾. Present estimates are that a third of dementia cases could possibly be prevented through lifestyle choices and by treating CVD risk factors, which would result in great human and economic cost savings⁽⁸⁾.

Reducing dementia risk or delaying dementia onset by treating these preventable risk factors could thus be an important focus for policies worldwide to reduce costs of care associated with dementia.

Importantly, however, longitudinal studies following people over time suggest that these CVD risk factors can change over the lifespan, with a drop in blood pressure and total cholesterol levels being more predictive of impeding onset of dementia in later life, than when these CVD risk factors are raised in midlife^(10,11). It is unclear why this is the case. It may be that pathology in the brain affects these parameters or other organs indirectly. It was hypothesised that these changes may also be caused by people forgetting to eat, which would lower body weight, blood pressure and total cholesterol. Reduced memory functions are often among the first signs of dementia⁽²⁾.

Folate and dementia

As such, it may also be why low blood folate has been associated with an increased risk for dementia⁽¹²⁾. People who have memory problems or mild cognitive impairment, which is a risk factor for dementia⁽¹³⁾ may forget to eat, which then affects nutrient intake.

Memory problems can also result in forgetting to brush teeth, which can affect dental health. The present research and that of others found that having fewer than ten teeth doubled dementia risk⁽¹⁴⁾. Dental disease is associated with infectious markers, which are now more recognised for their importance in promoting heart disease and dementia⁽¹⁴⁾. In the present studies these infectious factors (interleukins) were found to have independent associations with worse cognition and did not mediate the association of having few teeth with increased dementia risk⁽¹⁴⁾.

Many folate rich foods are chewy and not easy to masticate with few teeth. Green vegetables, liver, fibrous oranges and legumes, such as lentils, can contain high levels of folate. Vitamin B₁₂ has also been associated with cognitive function and is difficult to obtain for people who do not eat meat or animal protein and only small levels are present in whole grains and potatoes. In China, both green vegetable and meat consumption were found to have independent positive associations with memory function and a lower risk for dementia⁽¹⁵⁾. So it may be that low folate and/or low vitamin B₁₂ as a risk factor for dementia is associated with not having enough masticatory ability to break down foods to obtain these micronutrients. These B vitamin micronutrients are in turn associated with high homocysteine, a known risk factor for heart disease and dementia⁽¹⁶⁾. A meta-analysis showed that homocysteine levels could be reduced through treatment with folic acid and vitamin B₁₂⁽¹⁷⁾. In the prospective Kungsholmen and several other cohort studies following people over time, low folate or B₁₂ status was associated with an increased risk for dementia^(12,18).

However, folic acid treatment trials to improve cognitive function in people already afflicted with dementia have overall been unsuccessful. An early Cochrane review of four randomised controlled treatment trails did not find any evidence for improvement after folic acid with or without B₁₂ supplementation in people with cognitive impairment⁽¹⁹⁾. When another four studies were included in the meta-analyses some effect was found, but only in people with high homocysteine levels without dementia⁽¹⁷⁾. The study changing this meta-analyses outcome reported that memory and speed of information processing improved after folic acid supplementation for 2 years, but this was in people who did not have dementia at baseline and who were folate deficient⁽²⁰⁾. A later study not included in the Cochrane review also reported a small global cognitive improvement effect after a combination treatment of folic acid, B₁₂ and vitamin D for 2 years in older people (65+, *n* 2556) who did not have dementia at baseline and who had elevated homocysteine levels⁽²¹⁾. It could thus be the case that effects of folate supplementation on cognition are only found in people who are actually folate deficient, but do not have dementia.

It may be too late to improve cognition with treatment in people who are afflicted with severe dementia pathology. In an Oxfordshire based study, folic acid, vitamin B₆ and B₁₂ supplements given to people with mild cognitive impairment reduced brain atrophy by 30%,



particularly in the area that includes the hippocampus, the medial temporal lobe^(12,18). This area of the brain is the usually first to show atrophy in Alzheimer's disease, the most common type of dementia. In this study cognitive functions were not improved even though people did not have dementia yet.

Possibly, however, brain pathology was already too advanced in these people in the prodromal phases of dementia to show reversal of clinical signs. Alzheimer's pathology is thought to start long before clinical symptoms are present, possibly already in the fourth decade. A recent update of this study suggested *n*-3 fatty acid levels may need to be taken into account, as these may modify the outcomes. A meta-analysis of people with mild cognitive impairment or dementia showed only small effects of folic acid treatment in improving memory in people with mild cognitive impairment, but no other effects on any other cognitive tests or in people with dementia⁽²²⁾.

A meta-analysis of large treatment studies investigating older people without dementia or cognitive impairment also reported no overall effect of B vitamins in treatment trials. However, trends were seen for improved global cognitive function and memory⁽⁴⁾. Again this may be because some people included in the studies were not folate deficient. A small increased risk for colon cancer is seen with folic acid supplementation, so assessing whether people actually are deficient may be important. There may also be other potential adverse health risks of increasing folate⁽²³⁾.

Another related issue is folic acid fortification in starch. White and African-American elderly aged between 70 and 79 years of the observational Health, Aging and Body Composition longitudinal study⁽²⁴⁾ had a 9-year follow-up and 923 people underwent cognitive tests. Bloods were measured for homocysteine, folate and vitamin B₁₂. After fortification with folic acid, homocysteine levels did not reach critical levels associated with heart disease and dementia. In addition, an association between homocysteine or the B vitamins and cognitive decline was also not found. However, other cohorts have also not always found an association between B vitamins and cognitive decline/dementia. Because there were no data on this cohort before folic acid fortification was introduced, it is not possible to draw any firm conclusions from these analyses⁽²⁴⁾.

Soya and cognition

Similar inconsistencies are seen in cohort studies investigating soya products and dementia risk/cognitive function^(5,25). Phytoestrogens present in soya products can protect the hippocampus against β -amyloid induced neuronal damage, but also via positive effects on CVD parameters. In a recent review paper⁽²⁵⁾, of observational studies reviewed, only 23 % reported positive effects, 31 % found negative effects, 31 % found no effect of phytoestrogen consumption on cognition and 15 % found mixed effects. Negative associations of high tofu intake with a higher dementia risk and worse global cognitive

and memory function were found in Indonesian, Japanese American and Chinese populations aged 65 and over^(15,26-30). These associations were independent of socioeconomic status, education, age, or intake of other foods. However, one very large (>4700 patients) recent Chinese study investigating soya product consumption in the oldest old (here defined as those aged over 80 years) showed a 20 % lower risk of dementia in daily consumers *v.* never consumers⁽³¹⁾. Here, however, the focus was not solely on tofu as a soya product consumed and so there could be a mixture of fermented and non-fermented soya products, which may have different effects on the brain (see later). There was little resolution in the data (in the studies of East Asian people, most used soya products almost daily⁽²⁶⁾). A cut-off on the Mini Mental State Examination (of seventeen) was used to identify dementia rather than a validated dementia diagnoses and a continuous memory score. Similar to an earlier study in China, consumption of meat and vegetables (as well as fruit) decreased the risk of a low global cognitive score in this study⁽¹⁵⁾. The B vitamins in these foods could interact with soya phytoestrogen (see later). Total dietary patterns and interactions between foods should thus be investigated.

Lastly, the oldest old may have a different risk pattern as they are more resilient, having survived risk for heart disease, cancers and dementias. It may be that oestrogenic effects of soya products are different for this group⁽³²⁾.

Conversely, positive associations were also seen in other studies of East Asian elderly (Malaysian and Japanese^(33,34), respectively) when analysing total calculated isoflavone intake with executive function and attention (digit span), but not with memory or global cognition.

A negative association was reported for total isoflavone levels and memory⁽³⁵⁾, but here also positive associations were seen for speed of information processing in high isoflavone (phytoestrogens) consuming East Asian women living in the US; East Asian women in this cohort consumed twenty-five times the amount non-Asians did. No associations were reported in other cohorts, but it may have been that levels of calculated isoflavone intake were too low to exert effects⁽³⁶⁻³⁹⁾. This suggests that if tofu intake is investigated separately or whether total isoflavones are calculated from FFQ, when that intake is low, or which cognitive test is used, can all result in very different outcomes. Data suggest that effects may be more pronounced in East Asian populations, possibly because their habitual intake is overall usually higher. However, these higher isoflavone levels were not always found^(37,38) in studies of East Asians living in the USA. In addition, more East Asians produce equol from phytoestrogens in the gut, which is a highly potent oestrogenic metabolite⁽⁵⁾, but again this can be variable also within ethnic groups.

It is not entirely clear why high tofu intake would be associated with worse cognition and increased dementia risk. According to the Departments of Public Health at the Universities of Jakarta and Yogyakarta, Indonesia, formaldehyde was regularly added by vendors to tofu to preserve its freshness⁽²⁶⁾. Formaldehyde has been

shown to produce oxidative damage in the hippocampus and frontal cortex⁽⁴⁰⁾, both of which are important for learning and memory. Although added formaldehyde may explain why tofu negatively impacts on cognition, the present pilot study carried out with the Department of Public Health in Jakarta did not find any formaldehyde in tofu samples collected within the city⁽²⁶⁾. It may have been that this practice was abolished after it became outlawed.

Another theory was that tofu itself can exert negative effects on the brain through its effect on thyroid function. Preclinical hypothyroidism was seen to worsen with high tofu intake. Hypothyroidism is associated with lower cognition function and is relatively common, especially in older women⁽⁴¹⁾. However, when analysing this directly, thyroid function was not shown to mediate the negative association between high tofu intake and dementia risk⁽³⁰⁾.

As reported earlier, Greendale *et al.*⁽³⁵⁾ found that perimenopausal and postmenopausal Asian women with high isoflavone intakes had better processing speed, but worse verbal memory. The highest isoflavone consumers among non-Asians also had lower verbal memory scores during perimenopause. In a similarly aged female midlife population in Indonesia, curvilinear associations gave a better fit in the models (rather than negative or positive linear associations). There were clear optimal levels of genistein (the most potent oestrogenic isoflavone) associated with better memory functions⁽⁴²⁾. In contrast, a clear negative linear dose response existed for both genistein and tofu intake older people (65+) in China and Indonesia for memory^(15,26,42). Rice *et al.*⁽²⁸⁾ found worse effects on cognition if older (65+) Japanese American post-menopausal women were taking oestrogen treatment alongside high tofu intake. Negative associations of tofu with cognition were also more pronounced in elderly men (>68 years of age) if they had high levels of oestrogens⁽³⁰⁾. This could indicate that an oestrogenic environment confers a higher risk with tofu intake in older people, where optimal levels may exist for middle aged women depending on cognitive function and menopausal status.

Genistein and other isoflavones can act as agonists when oestrogen levels are low (post-menopause) but as antagonists when levels are high, as they only have half the receptor activity of oestrogens. The healthy-cell bias theory proposes that oestrogens can be neuroprotective when exposure occurs prior to the onset of neurodegeneration. However, if exposure takes place after neurons display damage (e.g. mitochondrial or damaged calcium channels, which is more likely in older people), oestrogens can accelerate self-programmed cell death. This mechanism is thought to be implicated in dementia and accelerated cognitive decline⁽⁴³⁾. In contrast, in women of middle-age who become oestrogen deficient because of the menopause, phytoestrogens present in tofu could protect against poor memory⁽⁴²⁾. Similar patterns exist for oestrogens in both observational studies and randomised controlled treatment trails⁽³²⁾.

Treatment studies using soya or phytoestrogen supplements have also shown variable effects^(5,25), but there is

no clear pattern. Of the randomised controlled treatment trails studies reviewed, a little more than half (53 %) reported that phytoestrogen intake (through diet or supplementation) had positive effects on cognition⁽²⁵⁾. However, 29 % found no effect, 6 % found negative effects and 12 % found mixed effects. Conversely, the present meta-analyses of large studies ($n > 50$) showed a small overall positive effect of soya supplements on memory⁽⁴⁾. This discrepancy may be related to differences in age of participants tested (as outlined) and the ethnic differences between studies, their ability to convert phytoestrogens into equol (the powerful oestrogenic compound formed in the gut), but could also be related to other foods in the diet of participants or type of cognitive tests used. Verbal memory may be most sensitive to oestrogenic treatments⁽³²⁾.

In contrast to tofu, tempe, a whole soyabean product that is fermented and contains B vitamins, such as folate and vitamin B₁₂, was found to improve memory and reduce dementia risk and amyloid and other dementia markers in both human observational studies and rodents^(26,27,44,45). The rodent studies showed that after ovariectomy, memory function decreased and β -amyloid levels increased. However, animals given tempe to treat the loss of oestrogens improved more than those given tofu or oestradiol on both dementia markers⁽⁴⁵⁾. In women undergoing oophorectomy (ovariectomy, removal of the ovaries) a dramatic decrease can be seen in memory functions, which can be reversed by oestradiol. Surgical menopause without oestrogen treatment before the natural age at menopause (about 50) can increase later life dementia risk⁽⁴⁶⁾.

Presently investigations on whether tempe can off-set memory decline in women undergoing oophorectomy and in those with dementia is ongoing. It may be that folate in tempe offsets potential negative effects of high levels of oestrogens⁽²⁷⁾. In the Oxford project To Investigate Memory and Ageing, older women who had high oestrogen levels were found to be at increased risk for dementia⁽⁴⁷⁾. However, if they also had high serum folate, they did not score below the cut-off scores on cognitive tests for dementia⁽⁴⁷⁾. It may be that folate protects against methylation implicated in age-related morbidity such as dementia. Future studies should take into account the whole diet of participants and interactions between foods, but also their genetic make-up and ability to metabolise some of these bioactive compounds. This personalised nutritional approach is gaining more in popularity.

Conclusions

The present review showed that there may be some effects of folic acid supplementation on cognition in older people who have no dementia at baseline and who are folate deficient. A meta analysis suggested that there may be a small positive effect of soya supplementation on memory. However, older East Asians may be at risk for dementia with high tofu consumption, where optimal levels may exist for middle-aged women.

Tempe, a fermented soya product, which contains folate and vitamin B₁₂, may have beneficial effects in increasing memory performance and randomised controlled treatment trials are now underway.

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Conflicts of Interest

None.

Authorship

E. H. formulated the research question, designed the studies, analysed or supervised analyses of most of the studies and wrote or co-wrote most of the articles referred to in the review. She was the main author on this review. S. K., A. K., M. S., and X. X. all worked on the projects mentioned in the review, helping to design the studies, analyse these and writing the initial drafts and papers while supervised on this by Professor Xiao Shifu (X. X.) and Professor Tri Budi Rahardjo (all) who also formulated research questions and design and who co-authored all papers referred to in the review. All authors contributed to this review.

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