

Invited paper

Alzheimer's and dementia: the nutrition connection

Patrick Holford BSc (Psych) Dip ION

Founder of the Institute for Optimum Nutrition, Director of the Mental Health Project,
Clinical Director of the Brain Bio Centre, London, UK

ABSTRACT

Abstract

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What could be worse than losing your mind, while your body has many years to run? Yet, that is precisely what happens to one in ten people over the age of 65, and one in two people over the age of 85. Currently in Britain half a million people suffer from Alzheimer's diseases (AD), costing the National Health Service £14 billion a year. With an ever-ageing population, the prediction is that, by 2030, 20% of people over 65, more than a million people in the UK, will have dementia or AD, the first symptoms of which are depression, irritability, confusion and forgetfulness. In the US the prediction is 13 million sufferers by 2050, according to the National Institute of Health.¹

A number of encouraging research avenues indicate that dementia and AD could be prevented, and even possibly reversed in the early stages by a comprehensive strategy using an optimum nutrition approach. One of the reasons this is possible is that new brain cells are being made all the time, even in old age and, under the right conditions, new brain cell growth can be encouraged.² Current research is focusing on how to encourage not only neuron growth, but also how to enhance the formation of new dendrite connections.

Contributory factors to the development of Alzheimer's disease

AD is a complex disease without a single cause, but with many contributors. Many researchers are now converging on the idea that it is a degenerative disease that develops largely due to the long-term consequence of faulty nutrition and exposure to anti-nutrients, plus certain negative lifestyle factors, much like cardiovascular disease, and that any long-term solution must involve fundamental changes to a person's diet. The contributory factors may include:

- a genetic predisposition
- viral infections
- inflammation
- lack of antioxidant nutrients
- lack of omega-3 fatty acids
- excessive stress and elevated cortisol
- raised homocysteine
- lack of B vitamins
- indigestion and/or malabsorption
- poor liver detoxification

- excess aluminium, copper and mercury
- acetylcholine and precursor deficiency.

Genetic predisposition and viral infection

Much research has focused on the gene, 'apolipoprotein E', or ApoE for short. It helps transport cholesterol and builds healthy membranes for the brain's neurons. Those who inherit a particular type of this gene, called ApoE4, have more than double the risk of developing AD. The presence of this defective gene is now being used as a marker to predict risk. However, it is not only the presence of this gene, but its activation that may incur risk, hence a hot area of research is into what activates ApoE4. Two candidates are infection and faulty nutrition. One of these is infection with the herpes simplex virus, according to research carried out at Manchester's Molecular Neurobiology Laboratory and reported in the *Lancet* in 1997.³ This research shows that viruses can damage genes and change the message they deliver to brain cells, causing cellular damage. The question then becomes: what protects your genes? Two mechanisms involved are enhanced methylation and improved oxidation-reduction. Another common polymorphism (MTHFR 677C>T) is of the *MTHFR* gene that encodes the key enzyme MTHFR, which converts homocysteine to methionine, discussed below; this polymorphism is a candidate for susceptibility to AD. However, enhanced nutrient status can mitigate this disadvantage.

Is Alzheimer's an inflammatory disease?

It is highly likely that both cardiovascular disease and AD result from the same or a similar disease process. Not only does the presence of cardiovascular disease greatly increase the chances of getting AD, especially if you have the ApoE4 gene, but many of the same causes apply to both conditions.⁴ Once cardiovascular disease is present, blockages in arteries may lead to a poor supply of key nutrients to the brain. Without a good supply of antioxidants, for example, brain cells become more vulnerable to free radical damage.

Cardiovascular disease is intimately linked to both a lack of antioxidants and excess exposure to oxidants, for example from fried food or from smoking cigarettes. Antioxidant nutrients such as vitamins C and E, have been shown to help both conditions; they not only mop up these brain pollutants, but also reduce inflammation.

The diagnostic proof of AD, as distinct from other forms of dementia, is the presence of plaques or patches of dead cells and other waste material in the brain. At the core of these plaques a substance called 'beta-amyloid' has been found. This is an abnormal protein that is also found in the plaques of arterial deposits. Beta-amyloid is a toxic invader that arises when the body is in 'emergency mode', resulting in inflammation, as the immune system becomes over-reactive. It's a scenario that develops once a person's total environmental overload exceeds their genetic capacity to adapt. Looked at in this way, the presence of the ApoE4 gene simply means less adaptive capacity to the insults of modern day diets and lifestyle, while optimum nutrition means more adaptive capacity by giving the brain and body a less toxic chemical environment. Inflammation, in this model, is the alarm bell.

This may explain why taking anti-inflammatory drugs offers some protection from AD, which is consistent with the hypothesis that the damage that occurs to brain cells is part of an overall inflammatory reaction. It also means that natural anti-inflammatory nutrients may prove to be important in prevention strategies, especially as cortisone-based anti-inflammatory drugs may make matters worse (see below).

If inflammation is the key, then, from a nutritional perspective, the way to prevent and reverse the brain damage that occurs in AD is to reduce causes of inflammation and increase natural anti-inflammatory nutrients, such as antioxidants and omega-3 fats. Inflammation can be caused by too many oxidants, too much homocysteine, digestive problems leading to poor liver detoxification and too much stress.

Antioxidants and Alzheimer's disease

Inflammatory reactions invariably mean increased production of oxidants, and hence an increased need for antioxidants such as vitamin A, beta-carotene, and vitamins C and E, all of which have been shown to be low in those with AD. Other antioxidants, including cysteine, glutathione, lipoic acid, anthocyanidins, and co-enzyme Q10, possibly other quinones, and melatonin may also prove to be important.

Both vitamin E and selenium have been shown to stop viruses from changing genetic messages, so one hypothesis is that only those deficient in these nutrients that are infected with certain viruses have an increased susceptibility to AD. This may partly explain why those who supplement vitamin E have a fraction of the risk of AD. A US study gave 633 disease-free 65-year-olds large amounts of either

vitamin E or vitamin C. A small number in each group would have been expected to show the signs of AD five years later. None did.⁵ Another study published in the *Journal of the American Medical Association* found that the risk of developing AD was 67% lower in those with a high dietary intake of vitamin E, versus those with a low intake.⁶

Vitamin E plays a key role not only in early prevention in this way, but also in slowing down the progression of the disease. In a landmark study reported in the *New England Journal of Medicine* in 1997, AD patients received either 2000 iu of vitamin E, the drug selegiline, or a placebo.⁷ Vitamin E was shown to reduce progression most significantly. Dr Leon Thal from the University of California, one of the doctors running this study, stated: 'The results of this study will be used to change the prescribing practices in the United States and probably many other parts of the world'. The American Psychiatric Association recommends vitamin E supplements for AD patients, however this is not common practice in the UK.

Omega-3 fatty acids

Also involved in calming down brain inflammation are the omega-3 fats, most prevalent in cold water, carnivorous fish such as salmon, tuna, herring and mackerel. As well as being anti-inflammatory, they are a vital component of brain cell membranes and help control calcium flow into and out of cells. This factor is important because too much calcium inside brain cells is known to contribute to the production of the toxic beta-amyloid protein.

Eating fish once a week reduces risk of developing AD by 60%, according to a recent study by Dr Martha Morris and colleagues from Chicago's Rush Institute for Healthy Ageing. They followed 815 people, aged 65 to 94 years, for 7 years and found that their dietary intake of fish was strongly linked to AD risk. They found that the strongest link was to the amount of DHA, a form of omega-3 fat found in fish. The greater a person's DHA intake, the lower their risk of developing AD. The lowest amount of DHA per day that offered some protection was 100 mg. EPA intake did not reach significance, however, as the highest intake of EPA consumed was 30 mg a day.⁸

Stress, cortisol and memory loss

Under prolonged stress, the body produces the adrenal hormone cortisol. The research of Professor Robert Sapolsky at Stanford University has shown that although cortisol is a powerful anti-inflammatory

hormone, raised cortisol can damage the brain. In studies with rats he found that two weeks of induced stress causing raised cortisol levels causes dendrites, the connections between brain cells, to shrivel up.⁹ He believes that brain cell loss in ageing and AD may be, in part, due to high levels of cortisol and recommends that corticosteroid drugs should not be used in AD patients for other medical problems like asthma or arthritis.¹⁰

Using a brain imaging technique, Douglas Bremner of Yale University has shown that the part of the brain responsible for learning and memory is smaller in patients with post-traumatic stress disorder, and that this correlates with poorer memory.¹¹ Researchers at the La Sapienza University have shown that cortisol levels are significantly higher in AD patients than in controls, and correlate with the severity of the disease.¹² Linda Carlson and colleagues at McGill University in Montreal have confirmed that in AD patients, the higher their cortisol, the worse their memory is. They also found that the higher their levels of dehydroepiandrosterone (DHEA) the better their memory was.^{13,14}

Adrenal exhaustion can also lead to a lack of cortisol, which increases inflammation. It's a question of balance. There is some evidence that DHEA may be helpful in restoring a normal balance of adrenal hormones in those with AD who have evidence of adrenal burnout. All this research implies that the ability to create a lifestyle that avoids non-stop stress is also important for reducing AD risk.

Homocysteine and B vitamin deficiency

Homocysteine is an example of a toxin that the brain can't protect itself against with optimum nutrition. It is made in the body from the normally beneficial amino acid methionine when a person is deficient in vitamin B6, B12, folic acid, or TMG.

The theory that homocysteine might be behind atherosclerosis and heart disease was first proposed by Dr Kilmer McCully back in 1969, and is now understood to be a major independent risk factor for cardiovascular disease. Dr Matsu Toshifumi and colleagues at Tohoku University, Japan, wondered if homocysteine was also damaging the brain. To check this they conducted brain scans on 153 elderly people and checked them against each individual's homocysteine level. The higher the homocysteine, the greater the damage to the brain.¹⁵ They also found that high homocysteine levels were strongly correlated with low folic acid levels. Other researchers have also found that older people with low levels of folic acid have an increased risk of developing AD, and Dr David Snowdon at the

University of Kentucky has confirmed by autopsies that the lower the levels of serum folic acid, the greater the neurological damage that person suffered.^{16,17}

A recent study in the *New England Journal of Medicine* charted the health of 1092 elderly people without dementia, measuring their homocysteine levels. Eight years later, 111 were diagnosed with dementia, of whom 83 were given the diagnosis of AD. Those with high blood homocysteine levels (above 14 $\mu\text{mol/l}$) had nearly double the risk of AD.¹⁸ More recently, evidence has emerged that even before there is evidence of declining mental function in so-called 'healthy' elderly individuals, high homocysteine also predicts physical degeneration in certain parts of the brain.¹⁹

A research group at the Baylor University Metabolic Disease Center in Dallas, Texas, led by Dr Teodoro Bottiglieri suggests that low levels of folate (leading to raised homocysteine) may cause brain damage that triggers dementia and AD. Their research has found that a third of those with both dementia and homocysteine levels above 14 $\mu\text{mol/l}$ are deficient in folate.²⁰

AD sufferers also tend to have less s-adenosyl methionine (SAME) in their brains, as well as higher levels of homocysteine in their blood.²¹ In Scotland, researchers have found that reduced mental performance in old age is strongly associated with high homocysteine and low levels of vitamins B12 and folate.²² They studied people who had taken part in the Scottish Mental Surveys of 1932 and 1947, which surveyed childhood intelligence. They found that while homocysteine was higher and mental performance weaker in the older group, the most mentally agile of either group had the highest levels of B vitamins and lowest levels of homocysteine. In the older group, high homocysteine accounted for a 7–8% decline in mental performance.²² Dr Andrew McCaddon has identified a genetic mutation, prevalent in Alzheimer's patients that leads to faulty methylation, and a functional B12 deficiency.²³

The accumulating evidence points to a consistent pattern: the higher a person's homocysteine level and the lower their B vitamin status, particularly folic acid, B12 and B6, the greater their chances of dementia and AD. Exactly how high homocysteine, B vitamin, and SAME deficiencies might contribute to the kind of brain damage seen in AD is a key current research question. Since raised homocysteine and poor B vitamin status are indicators of poor methylation, and since an estimated one in four gene mutations are the result of faulty methylation, homocysteine metabolism may shed light of the gene–environment interaction as a contributor to AD. Although the homocysteine link is in the early stages of research it certainly makes

sense to ensure an optimal intake of B6, B12 and folic acid in older people, meaning 20 mg, 50 μg and 1000 μg a day, respectively.

B vitamins do far more for the brain than reduce homocysteine levels. Oxygen transport depends on vitamin B12, folic acid, niacin, and essential fats being transported to and used by the brain. Vitamin B1 deficiency has long been known to result in brain damage. One of the most dangerous problems of excessive alcohol consumption is induced B1 deficiency. The condition is called Wernicke–Korsakof syndrome. The symptoms include anxiety and depression, obsessive thinking, confusion, defective memory (especially of recent events) and time distortion – not so different from AD. Vitamin B3 (niacin) is crucial for oxygen utilisation. It is incorporated into the co-enzyme nicotinamide adenosine dinucleotide (NAD), and many reactions involving oxygen need NAD. Without it, pellagra and senility can develop. For these reasons, an optimal intake of all the B vitamins is an important part of an AD prevention strategy.

Indigestion, malabsorption and poor liver detoxification

B vitamin deficiency is not only a function of poor diet, but also poor absorption, both of which are prevalent in the elderly with dementia and AD. Although vastly underexplored, hypochlorhydria is also a common feature of old age and may impact on amino acid absorption and neurotransmitter levels. An extensive review of nine vitamins in the *Journal of the American Medical Association* in 2003 showed that elderly people, vegans, alcohol-dependent individuals, and patients with malabsorption are at higher risk of inadequate intake or absorption of several vitamins.²⁴ Elderly persons are more likely to have low values for serum and erythrocyte folate, and for serum cobalamin, and many of those with low vitamin levels have biochemical abnormalities consistent with true deficiency, including raised homocysteine.²⁵ Therapy with the appropriate vitamin reverses the biochemical defect, however the amount required is often substantially in excess of the recommended daily amount (RDA). For example, 10 μg of vitamin B12 is ineffective in restoring B12 status in those with low or borderline serum B12, while 50 μg per day is both effective in restoring B12 status and lowering homocysteine levels.²⁶ Assuming adequacy from calculations of dietary intake is also suspect in the light of recent research indicating wide variation in absorption of folate from foods, and evidence that folic acid in supplements is as much as three times more effective in raising blood levels

of folate and lowering homocysteine levels than the equivalent amount of folate in food.²⁷

It is highly likely that inadequate diet, coupled with digestive and absorptive problems, may lead to poor nutrition and impaired liver detoxification, an increased toxic load on the brain, increased inflammation and a predisposition towards dementia and AD. This would imply that nutrients that improve digestion, absorption, and detoxification might help those with dementia and AD. This includes the amino acids l-glutamine, cysteine, and glutathione.

Aluminium, mercury and copper

Another brain toxin found in the plaques of AD sufferers is aluminium. While plenty of studies have shown this increased accumulation of aluminium, what isn't clear is whether this is a cause or a consequence of the disease. The likelihood is that it's a bit of both and still a significant contributor to memory problems. Numerous epidemiological surveys have linked aluminium intake in water to increased risk of AD. Other sources (food, medicines, toiletries and cosmetics) are less well investigated. In a study in the 1980s of 647 Canadian gold miners who had routinely inhaled aluminium since the 1940s (this used to be a common practice, thought to prevent silica poisoning), all tested in the 'impaired' range for cognitive function, suggesting a clear link between aluminium and memory loss.²⁸ A number of recent review papers have kept aluminium firmly on the map of potential contributors to dementia and AD.^{29,30} While the mechanism for action of aluminium in brain degeneration is far from clear, aluminium does exert a pro-oxidant effect in combination with copper, but not an inflammatory effect.³¹

Beta-amyloid is a metalloprotein that contains zinc, copper, and iron. One hypothetical cause of its build up and neurotoxic effect is that it mops up surplus metals and that these metals make beta-amyloid produce more hydrogen peroxide, a toxic free radical linked to its neurotoxic effect. Copper encourages this effect, while zinc appears to render beta-amyloid less harmful. This hypothesis, proposed by Dr Ashley Bush from Harvard Medical School, and colleagues from the University of Melbourne, Australia, has only been put to the test in a small randomised trial, giving AD patients clioquinol, a drug that prevents copper and zinc binding to beta-amyloid, thereby potentially promoting its dissolution and diminishing its toxic properties. This resulted in a reduction in deterioration of AD patients compared with those receiving placebos.³² This line of investigation is likely to encourage

further research into the possible toxic effects of copper and protective effects of zinc.

Mercury is another potential cause for concern. Autopsies of brains from AD patients, compared with control patients of the same age, have shown raised levels of mercury.³³ Researchers from the University of Basel, Switzerland, have also found high blood mercury levels, more than double those of the control groups, in AD patients, with early-onset AD patients having the highest mercury levels of all.³⁴ Trace amounts of mercury can cause the type of damage to nerves that is characteristic of AD, according to recent research at the University of Calgary Faculty of Medicine, strongly suggesting that the small amounts we are exposed to, for example from amalgam fillings, may be contributing to memory loss.³⁵ Although the research on the link of mercury to AD is in its infancy, it is certainly logical to reduce exposure to this highly toxic metal.

Acetylcholine enhancers and memory

Whatever the contributory causes to the brain damage seen in AD, once the brain damage occurs, there is memory loss. Understanding how that occurs opens up avenues for treatment.

A memory is not held in one, but in several brain cells joined together in a network. The memory itself is thought to be put into storage by the neurotransmitter acetylcholine, and stored by altering the structure of a molecule, RNA, within brain cells. The limbic system, which is the 'doughnut' on top of the brain stem, then has to decide if the memory is worth keeping. The amygdala, part of the limbic system, decides about more emotional memories, while the hippocampus decides about others. In AD the hippocampus loses its ability to file memories, resulting in an inability to create new ones. People with AD also show marked deficiencies in acetylcholine, no doubt largely because these acetylcholine-producing brain cells have been damaged or destroyed. Even if a memory is intact, without sufficient acetylcholine one cannot connect one part of the memory with others. For example, you know the face but can't remember the name.

Most currently prescribed medication for dementia and AD block the breakdown or re-uptake of acetylcholine. An alternative approach would be to supplement the nutrients the brain uses to make acetylcholine in the first place. The primary precursor nutrient is phosphatidyl choline, the conversion of which is dependent on pantothenic acid (vitamin B5). However, phosphatidyl choline is synthesised from phosphatidyl dimethylaminoethanol (DMAE), itself synthesised from phosphatidyl ethanolamine (PE) and phosphatidyl serine (PS),

reactions dependent on good methylation, requiring sufficient *S*-adenosyl methionine (SAM) and magnesium. While each of these nutrients has demonstrated mild memory-promoting effects the combined therapeutic effect of these 'acetylcholine-friendly' nutrients has yet to be adequately explored in the prevention or treatment of AD patients.³⁶

Also of interest in the amino acid pyroglutamate, from which the drug piracetam (and various other nootropic drugs) is derived. Early animal research has indicated a potential to increase acetylcholine reception.³⁷ A recent meta-analysis of studies demonstrates a difference between those individuals treated with piracetam and those given placebo.³⁸

Herbs: ginkgo biloba and vinpocetine

The herbs ginkgo biloba and the herbal extract vinpocetine, have also demonstrated potential memory enhancing effects in the elderly. While a Cochrane Review in 2002 concluded 'promising evidence of improvement in cognition and function with ginkgo' three recent randomized trials on ginkgo have failed to confirm earlier positive results for those with cognitive impairment however one showed mild improvement for those who were cognitively intact.³⁹⁻⁴² Ginkgo may therefore have a role to play in prevention. Research on vinpocetine, an extract of the periwinkle plant, is also promising, but in its infancy.⁴³

An optimum nutrition approach to Alzheimer's disease

The optimum nutrition approach to the prevention of age-related memory decline, dementia and AD is based upon minimising potential negative effects and guaranteeing an optimal intake of potentially protective nutrients through diet and supplementation. In practical terms this strategy means:

Diet

- Maximise intake of fresh fruit and vegetables, preferably organic, high in antioxidant nutrients, and wholefoods, high in B vitamins.
- Eat seeds and nuts, high in vitamin E.
- Eat cold-water, carnivorous fish, preferably not wild, from the Atlantic, or, at least, organic (NB care is needed to limit exposure dependent on mercury load).

- Minimise deep-fried food and burnt meat, high in oxidants.
- Minimise alcohol consumption.
- Drink filtered or bottled water (lower in copper and aluminium).

Lifestyle

- Minimise exposure to mercury, including amalgam fillings and excessive carnivorous fish consumption.
- Minimise exposure to aluminium (unfiltered water, old style pots and pans, food cooked directly on aluminium foil, cosmetics, toiletries containing aluminium salts).
- Avoid smoking and passive smoking.
- Minimise stress.

Supplements

- Multivitamin including B6 10 mg, B12 10 µg, folate 400 µg, zinc 10 mg.
- Vitamin C 1000 mg.
- Vitamin E 600 mg.
- If homocysteine is above 9 increase B6 to 20 mg, B12 to 50 µg, folic acid to 1000 µg.
- Omega-3-rich fish oil, providing docosahexenoic acid (DHA) 400 mg, EPA 400 mg.
- Possibly beneficial: phosphatidyl serine, phosphatidyl choline, ginkgo biloba.

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CONFLICTS OF INTEREST

None.

ADDRESS FOR CORRESPONDENCE

Patrick Holford, Mental Health Project, Carters Yard, London SW18 4JR, UK. Tel: +44 (0)20 8871 2949; fax: +44 (0)20 8874 5003; email: pat@patrickholford.com

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