ELEVATED HOMOCYSTEINE

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HELEN BROWN

Dissertation on Elevated Homocysteine

Introduction
Elevated homocysteine levels are linked to a wide range of illnesses, including cardiovascular disease, cancer, autoimmune conditions, osteoporosis and Parkinson's Disease. An explanation of why elevated homocysteine is a problem and how reducing it may provide symptom improvements follows. To demonstrate the various ways elevated homocysteine may damage health there is a more detailed discussion in relation to Alzheimer's disease and clinical depression.

1. What is Homocysteine?

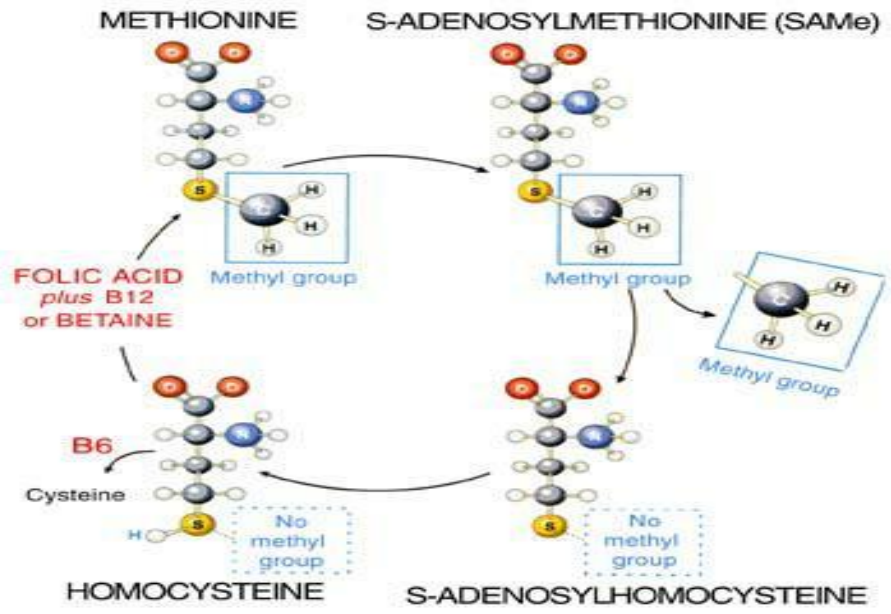
It is a naturally occurring, sulphur containing non-protein amino acid, which is needed by the body in small amounts for protein synthesis and detoxification. It is an inflammatory substance and can become toxic in the body if levels are out of optimal range. Its levels in the body are increasingly being regarded as a reliable predictor of health and longevity.

2. How is homocysteine formed?

It is biosynthesised in the body from the essential amino acid methionine, obtained mainly from animal protein, in a complex biochemical process known as methylation. This is a vital metabolic process in which methyl groups, comprising one carbon and three hydrogen molecules, are systematically transferred by enzymes, some of which add, others which remove and some which replace methyl groups onto proteins, enzymes and DNA repeatedly in every cell in the body, billions of times per second. This allows cell genes to be regulated, toxins and chemicals to be detoxified, neurotransmitters, (messengers between nerve cells), such as dopamine to be made, fatty acids to be processed, hormones such as oestrogen to be processed and metabolised correctly, many important compounds like betaine, choline and adrenal hormones to be synthesised, immune T and natural killer cells to be made, DNA and RNA to be synthesised, cell energy to be produced and nerve myelination to occur.

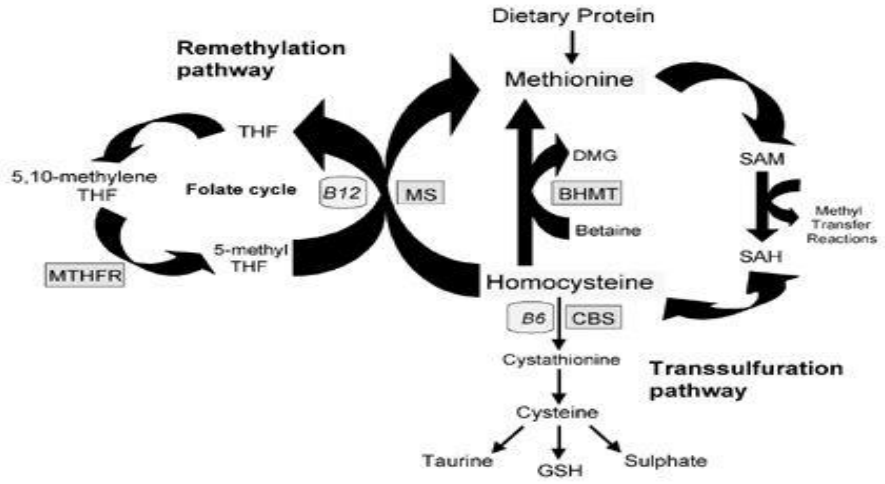
As well as being completely dependent on a variety of enzymes, methylation also relies on sufficient amounts of key nutrients: Vitamin B12, folate (B9), Vitamin B6, as well as niacin (B3), riboflavin (B2), magnesium and zinc. In methionine methylation, (or one-carbon metabolism), the enzyme methionine adenosyltransferase enables methionine to react with the body's energy currency, ATP, to form SAMe, (S-adenosyl methionine), the 'activated' form of methionine. SAMe is a critical methyl donor required for most methylation reactions in the body. During methylation SAMe donates its methyl groups to activate other reactions, eventually becoming homocysteine.
However, when the methylation process is working efficiently homocysteine is metabolised into more useful amino acids in one of two ways:
a) via a remethylation pathway it is regenerated using the enzyme methionine synthase (MS), into methionine, then SAMe. Using Vitamin B12 as a co-factor homocysteine accepts a methyl group from 5-MTHF (5-methyltetrahydrofolate) obtained from dietary folates; riboflavin and zinc are also required. Success in this pathway is highly dependent on proper functioning of the enzyme MTHFR (methylenetetrahydrofolate reductase). In an alternate route remethylation can occur, mainly in the liver and kidneys, via the BHMT (betaine-homocysteine methyltransferase) enzyme which uses a methyl group from betaine (Trimethylglycine,TMG).
b) via a Transsulfuration pathway, occurring only in the liver, kidneys, small intestine and pancreas, homocysteine is firstly converted to cystathione by the enzyme CBS (Cystathionine-beta-synthase), before being converted into amino acid cysteine. Vitamin B6 is an essential cofactor in this conversion, together with riboflavin and zinc. With the help of another enzyme, Cystathionine Lyase, cysteine can be converted into the master antioxidant glutathione (GSH) as well as the antioxidant and major detoxifier taurine. Protein synthesis can then take place. Normally approximately 50% of dietary methionine is remethylated and the remainder is transsulfurated to cysteine. See diagrams 1 and 2 below.

Diagram 1



http://www.lifeextension.com/Magazine/1998/8/report2/Page-01

Diagram 2



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3. What are considered high levels and when do they rise?

Levels have not been set officially but many believe that levels over 10 µmol/L, are unhealthy, while some practitioners consider 7 µmol/L, the highest acceptable amount. Some laboratory tests have set higher normal levels, typically under 13 µmol/L. Men generally have higher levels than premenopausal women because oestrogen lowers homocysteine, but levels rise in women after menopause.
If methylation is working well homocysteine is recycled back to methionine, then SAMe using Vitamin B12 and folate or detoxified and converted to cysteine, then glutathione, using Vitamin B6. Homocysteine levels reflect how well detoxication and methylation are working within all cells, 2 critically important aspects of metabolism. If methylation is poor SAMe and glutathione production decreases, and more homocysteine accumulates in the blood causing inflammatory damage.

4. What factors raise homocysteine by inhibiting methylation?

a) A diet too high in foods containing methionine like red meat, especially ones high in processed fats, and too many dairy products and eggs, which contain large amounts of arachidonic acid, from which pro-inflammatory prostaglandins are produced. The problem is exacerbated when B vitamin intake is low. Emphasis should be on eating a wide variety of proteins including grass fed meats and oily fish, organically reared, pulses, nuts and seeds. Paradoxically where the diet is too low in methionine homocysteine can also rise.

b) Dietary deficiencies in any of the main nutrients supporting the methylation cycle - vitamins B6, B12, folate (B9), choline and betaine, as well as riboflavin, niacin, magnesium and zinc, may impair remethylation and transsulfuration processes resulting in abnormally high homocysteine levels. B vitamins are interdependent, water soluble and most need to be replenished regularly.

(i) Vitamin B6 is essential for protein synthesis, neurotransmitter and red blood cell production. It is vital for avoiding an accumulation of homocysteine and for glutathione production. If the body is deficient in folate, vitamin B12 or if a MTHFR gene defect is present homocysteine levels rise increasing demand for vitamin B6 to lower it. It needs sufficient riboflavin and zinc to be activated. [1] Good food sources include bananas, fish, nuts, seeds and whole grains.

(ii) Folates are key in the methylation cycle and very important for protein and DNA synthesis, amino acid metabolism and mental health. Good sources are liver, fresh oranges and green leafy vegetables, but folates can be easily destroyed in cooking. Although red blood cells can retain folate it is not well transported to the brain and is quickly eliminated from the central nervous system. Many foods are now fortified with synthetic folic acid, but it must go through several biochemical changes to become usable in the body as 5-MTHF (also called L-Methylfolate). Individuals with low methionine intake, low stomach acid (below), defective genes (below) or low vitamin B12 levels have difficulty making this conversion, meaning folates can become ‘trapped’ in a form unusable in the body. Also, excess folates can mask a vitamin B12 deficiency.

(iii) Vitamin B12 (cobalamin) is crucial for normal red blood cells production, cell metabolism, DNA synthesis, energy production, maintenance of nerve fibres and neurotransmitter synthesis. In the elderly deficiencies can cause memory impairment mimicking Alzheimer’s disease. It is also needed for proper cardiovascular, digestive and immune function. Most significantly it works jointly with folate to reduce homocysteine levels, thereby keeping SAMe levels high and encouraging good detoxification for the entire body through the transulfuration pathway. However, without sufficient vitamin B12 to enable the enzyme methionine synthase to convert folate into its usable form, 5-MTHF, folate deficiency will occur even though body folate levels may be adequate. Theoretically, healthy adults consuming animal produce regularly should not be deficient because more than 2500 µg can be stored in the body, requiring only a small daily intake of 2.4µg to maintain adequate amounts. However, a study of adults aged between 26 and 83, carried out in the United States, suggested that 40% of people may have low to normal vitamin B12 levels, 9% being seriously deficient, even among younger individuals. Almost half of the over 60 age group were deficient. [2]

Individuals following strict vegetarian diets can become deficient in vitamin B12, as the most bioavailable form, methycobalamin, is found exclusively in animal products, richest sources including organic meat, dairy produce and eggs. Foods like spirulina contain Vitamin B12 ‘analogues’, a form the body cannot

[1] Suzy Cohen Drug Muggers 2011

[2] https://www.ars.usda.gov/news-events/news/research-news/2000/b12-deficiency-may-be-more-widespread-than-thought/

use, which may prevent uptake of actual vitamin B12. A report using data from 18 studies found that individuals who had followed a vegetarian diet from birth were most deficient. [3]

(iv) Choline is needed to make the methyl donor betaine, which contributes about 60% of methyl groups for homocysteine metabolism, particularly important when alcohol and methionine consumption is high and folate intake is low. [4] Choline is also essential for cell membrane signalling (phospholipids) and for synthesis and maintenance of the neurotransmitter acetylcholine, vital for memory and learning. Richest food sources are eggs, meat, poultry, fish, cruciferous vegetables and dairy. Generally, dietary intake has been found to be inadequate [5] , but this may be due to absorption problems related to genetic defects. A large study found that adults with the highest choline and betaine intake had the lowest amounts of inflammation in the body, while those consuming the most betaine had 10% lower concentrations of homocysteine than those eating the least. Betaine is abundant in wheat, quinoa, spinach and beetroot. [6]

c) Problems with absorption. It is more difficult to absorb and assimilate all B vitamins, particularly vitamin B12, if stomach, pancreas and small intestine function is poor, especially in conditions like Crohn's disease, celiac disease, small intestinal bowel overgrowth (SIBO) or parasitic infections like H. Pylori, which often correlate with low stomach acid production. Inadequate gastric acid impairs vitamin B12 absorption significantly, because it means intrinsic factor, made in the stomach, with which vitamin B12 must combine to be absorbed further down the digestive tract, cannot be produced either. Without intrinsic factor only 1% of vitamin B12 can be absorbed, even though blood levels may appear normal. Ageing decreases production of both gastric acid and intrinsic factor, which can lead to severe deficiencies in the elderly.

d) Many medications deplete the body of B vitamins needed in methylation. For example, long term use of antacids, proton pump inhibitors (PPI's) which reduce stomach acid production, certain antibiotics, hormone replacement therapy (HRT), oral contraceptives, Metformin for diabetes all deplete vitamin B6, B12 and folates.[7] One study found that patients who had used PPI's for over 2 years had a 65% increased likelihood of being Vitamin B12 deficient, effects being more noticeable at higher doses and in younger people.[8] Methotrexate used for some autoimmune conditions disrupts folate metabolism.[9]

e) Smoking inactivates vitamin B6 and depletes body folate and vitamin B12 stores, needed in methylation. It also increases oxidative stress.[10] Individuals smoking over 20 cigarettes daily had homocysteine levels 18 % higher on average than non-smokers. [11] Only complete cessation reduces homocysteine levels. [12]

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[3] Nutr Rev. 2013 Feb;71(2): How prevalent is vitamin B(12) deficiency among vegetarians? Pawlak R[1], Parrott SJ, Raj S, Cullum-Dugan D, Lucus D

[4] Nutrients. 2013.The metabolic burden of methyl donor deficiency with focus on the betaine homocysteine methyltransferase pathway**.** Obeid R[1].

[5] Nutr Rev 2009 Choline: An Essential Nutrient for Public Health. Steven Zeisel

[6] (Am J Clin Nutr. 2008 Feb;87(2):424-30.Dietary choline and betaine intakes in relation to concentrations of inflammatory markers in healthy adults: the ATTICA study. Detopoulou P[1], Panagiotakos DB, Antonopoulou S, Pitsavos C, Stefanadis C).

[7] Drug Muggers. Suzy Cohen

[8] https://well.blogs.nytimes.com/2013/12/10/acid-suppressing-drugs-linked-to-vitamin-b12-deficiency/?_php=true&_type=blogs&_r=0

[9] Mol Med. 2012; 18(1): 423–432. Low-Dose Methotrexate Inhibits Methionine *S*-Adenosyltransferase *In Vitro* and *In Vivo.* Yi-Cheng Wang and En-Pei Isabel Chiang

[10] ***Marszałł M[1], Czarnowski W*** Smoking influence on the level of homocysteine and 5-methyltetrahydrofolic acid in active and non smokers, Przegl Lek [translation: Drug Overview], 2007

[11] International Journal for Vitamin and Nutrition Research 69(5):322-9 · October 1999 Epidemiologic Correlates of Serum Folate a**nd h**omocysteine Levels among Users and Non-users of Vitamin Supplement Kato I[1], Dnistrian AM, Schwartz M, Toniolo P, Koenig K, Shore RE, Zeleniuch-Jacquotte A, Akhmedkhanov A, Riboli E.

[12] Clin Cardiol. 2002 Jan;25(1):23-6. Smoking cessation, but not smoking reduction, reduces plasma homocysteine levels. Stein JH[1], Bushara M, Bushara K, McBride PE,Jorenby DE, Fiore MC.

f) Excessive alcohol consumption can seriously hinder absorption of all B vitamins, particularly vitamin B6, from the intestines. Effects are more serious if a defective gene has been inherited. [13] High coffee consumption, over 4 strong cups daily, also raises levels. [14]

g) Kidney dysfunction increases homocysteine because tiny filters (glomeruli) in the kidneys are responsible for removing toxins, like homocysteine, from the blood. Persistently high levels, despite taking homocysteine lowering nutrients, may indicate dysfunction.

h) Low thyroid hormone levels, psoriasis, obesity, too little or excessive exercise all raise homocysteine levels.

i) Genetic mutations affect ability to methylate by altering enzyme activity. Defects can be inherited from one parent (heterozygous) or from both (homozygous). Numerous defect variations, called SNPs (single nucleotide polymorphisms) can occur within all three main enzymes involved in homocysteine metabolism: methionine synthase (MS) and 5methyltetrahydrofolate reductase (MTHFR) in re-methylation, and cystathionine β-synthase (CBS) in transsulfuration. Different polymorphisms may co-exist in an individual.

In a rare genetic condition called homozygous homocystinuria, affecting about one in 200,000 people, defects in the vitamin B6 dependent CBS enzyme causes dangerously high homocysteine accumulations and severe early onset cardiovascular disease. Lifelong supplementation with vitamin B6 is essential. In heterozygous homocystinuria, affecting one in 200 people, CBS works inefficiently leading to raised homocysteine. Any genetic defect in the CBS enzyme, impairing ability to detoxify homocysteine, can lead to decreased glutathione production. [15]

Mutations in the vitamin B12 dependent MTRR gene can impair activity of the enzyme methionine synthase needed to activate folates.

Genetic defects in the MTHFR C677T mutation are the most widely researched and are common in certain ethnic and geographic populations. In the United States, approximately 20% to 40% of white and Hispanic individuals, but only 1-2% of blacks, are heterozygous, and in North America, Europe, and Australia, roughly 8% to 20% of the population are homozygous. In individuals with one SNP, enzyme ability to methylate folic acid is reduced to approximately 65% of normal, whereas those who have two SNPs have only 30% of normal enzyme function. [16]

MTHFR defects increase folate and riboflavin requirements. Although synthetic folic acid is very effective at reducing neural tube defects it needs good digestive function, making it harder for older individuals to break down. This can lead to harmful accumulations. Active forms of folate, 5-MTHF and L-Methylfolate, have several advantages over folic acid and could therefore reduce homocysteine more effectively. They provide plasma folate levels up to 700% higher, are unlikely to hide a vitamin B12 deficiency and can cross the blood-brain barrier. [17]

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[13] Alcohol. 2001 Oct;25(2):59-*High prevalence of hyperhomocysteinemia in chronic alcoholism: the importance of the thermolabile form of the enzyme methylenetetrahydrofolate reductase (MTHFR).* de la Vega MJ et al

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Christensen B[1], Mosdol A, Retterstol L, Landaas S, Thelle DS

[15] M. Mcevoy – Methylation, Epigenetics and Nutrigenomics: Identifying and correcting the core issues in disease March 2013 Metabolic Healing

[16] Circulation. July 6, 2015 Homocysteine and MTHFR Mutations Stephan Moll, Elizabeth A. Varga

[17] http://www.lifeextension.com/magazine/2009/8/Is-Homocysteine-Making-You-Sick/Page-02

5. Dangerous effects of homocysteine when elevated

a) Homocysteine accelerates oxidation and cell ageing. Pollutants, excessive stress and even normal metabolic processes, like energy production constantly produce free radicals (oxidants), unstable forms of oxygen. Rate of ageing largely depends on how well the body can protect its tissues against them. High homocysteine greatly increases free-radical oxidation causing cell damage, both as an inflammatory substance and by severely depleting glutathione availability due to poor methylation. Glutathione, which declines with age, works within cell mitochondria as a potent antioxidant neutralising and detoxifying free radicals, repairing cell DNA and playing an essential role in immune function. Without sufficient glutathione, toxins overload the liver and fat-soluble toxins may be stored in fatty tissues, particularly the central nervous system, breasts and prostrate. [18] Severely depleted levels, found in many chronic illnesses like Alzheimer's disease, chronic fatigue syndrome, cancer and rheumatoid arthritis, prevent folic acid and vitamin B12 from being used in the body (functional deficiency) because they need sufficient glutathione to be changed into their active form. Further glutathione depletion then results from these vitamin deficiencies [19](Methionine- glutathione block hypothesis)

b) Homocysteine can overstimulate NMDA (N-methyl-D-aspartate) receptors leading to excessive glutamate production. Glutamate is the body's most common excitatory neurotransmitter, helping electrical impulses to travel along nerves. It is abundant in the brain, particularly in the memory centre, and is needed to make folate and important amino acids like arginine, glutathione and GABA. However excessive glutamate is harmful because it destroys glutathione and promotes cell death.

c) Homocysteine increases inflammation and pain. Excessive and persistent inflammation is destructive and a major cause of all chronic diseases. It can lead to permanent damage to various tissues, like arteries and nerves. Elevated homocysteine levels in the blood cause excessive inflammation by encouraging higher blood levels of arachidonic acid and prostaglandin E2, chemicals which are used to promote inflammation. [20]

d) By binding with proteins homocysteine can create modified proteins called homocysteine-thiolactone and N-homocysteinylated protein. Homocysteine-thiolactone attacks many other types of protein, including those in the blood.[21] The immune system may not recognize modified proteins and attack them, leading to inflammation and autoimmunity. [22]

e) Homocysteine can cause arterial damage (atherosclerosis) in several ways. It damages arterial walls causing fatty acids to accumulate around the lesions. Circulating immune cells (monocytes) rush to the injury sites, creating inflammation. Arterial cells multiply as they attempt to repair the lesions, which encourages increasingly thick oxidised cholesterol plaques (homocysteinylated lipoproteins) to accumulate on vessel linings. [23] [24]Arteries gradually become narrower and more rigid. Homocysteine also encourages blood platelets to clot and reduces supply of nitric oxide (essential to maintain good blood flow). [25] Thicker blood and narrower, less flexible arteries can raise blood pressure and

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[18] https://drjockers.com/glutathione-levels/

[19] Amino Acid Report: Discover the power of vegetarian protein (4 Aug 2016) by Linda Lazarides

[20] Eur J Clin Invest. 2002 Effect of homocysteine on arachidonic acid release in human platelets**.** Signorello MG[1], Pascale R, Leoncini G.

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[24] https://drjockers.com/homocysteine-levels/

[25] *Nitric Oxide. 2009 Homocysteine decreases platelet NO level via protein kinase C activation. Signorello MG et al).*

significantly impair blood flow and oxygen to the heart, brain and other areas of the body, increasing the risk of heart attacks, strokes, deep vein thrombosis and pulmonary embolism.

f) Homocysteine can cause brain damage. The brain is always active so the brain microcirculation, a dense network of blood vessels, relies on a constant supply of oxygen and nutrients, particularly folates and omega 3 fatty acids. High amounts of oxygen, unsaturated fats and comparatively poor antioxidant systems make it particularly vulnerable to oxidative damage, greatly increasing glutathione requirements. The brain is normally protected from oxidative stress and chronic inflammation by the blood-brain barrier, designed to allow entry to only small nutrients. Elevated levels of homocysteine are neurotoxic to the brain causing 'leaky brain', where the barrier is breached, allowing entry to harmful substances which cause neurological damage and oxidative stress. [26]

By damaging arteries homocysteine may also reduce blood flow to the brain microcirculation, causing red blood cells to clump together or micro clots to form in smaller blood vessels. As blockages develop neurons may be damaged by mini strokes or silent brain infarctions (cerebrovascular disease) or lost because oxygen and nutrients cannot reach brain cells effectively, leading to memory loss and dementia**,** such as Alzheimer's disease **[27]**

6. Alzheimer's disease

Alzheimer's disease is the most common type of dementia, often coexisting with other types of dementia. Although found primarily in older adults, brain changes start decades before symptoms show. Starting with intermittent memory loss (mild cognitive impairment), progressive cognitive loss occurs. It is estimated that 16% of people over 70 years old have mild cognitive impairment (MCI) and half of them will develop Alzheimer's disease. [28]

It mainly affects the hippocampus, where new memories are formed, and cerebral cortex areas involved with thought, planning and remembering. In brain tissues two significant changes occur which lead to neuron death, loss of connections (synapses) between neurons and significant brain shrinkage, especially in the hippocampus. a) Neurofibrillary tangles form within neurons. These are mainly composed of abnormal twisted remnants of tau protein, which disrupt normal cell structure and function. b) Beta amyloid protein (derived from amyloid precursor protein(APP) and normally broken down and eliminated in a healthy brain) accumulates into hard insoluble plaques between neurons.

Several studies have found evidence linking homocysteine to the disease process. A meta-analysis found that although numbers of amyloid plaques seem to increase naturally with ageing, high homocysteine levels may accelerate their formation by increasing oxygen free radicals which enhance production of beta amyloid protein. [29] Another study suggests homocysteine thiolactone worsens Alzheimer's disease by encouraging fibrinogen, (a blood clotting protein), and beta amyloid deposits to interact to form tight blood clots. [30] Results from an autopsy study of brain tissue from 265 deceased

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[26] (Blood. 2006 Jan 15; 107(2): 591–593. Prepublished online 2005 Sep 27. doi: 10.1182/blood-2005-06-2506Elevated levels of homocysteine compromise blood-brain barrier integrity in mice Atul F. Kamath, Anil K. Chauhan, Janka Kisucka, Vandana S. Dole, Joseph Loscalzo, Diane E. Handy, and Denisa D. Wagner)

[27] JAMA-JOURNAL OF THE AMERICAN MEDICAL ASSOCIATION Volume: 277) Brain infarction and the clinical expression of Alzheimer disease - The nun study Snowdon DA[1], Greiner LH, Mortimer JA, Riley KP, Greiner PA, Markesbery WR.

[28] PLoS One. 2010 Homocysteine-lowering by B vitamins slows the rate of accelerated brain atrophy in mild cognitive impairment: a randomized controlled trial.Smith AD[1], Smith SM, de Jager CA, Whitbread P, Johnston C, Agacinski G, Oulhaj A, Bradley KM, Jacoby R, Refsum H.

[29] Int J Clin Exp Med. 2014 Meta-analysis of plasma homocysteine content and cognitive function in elderly patients with Alzheimer's disease and vascular dementia. Wang B[1], Zhong Y et al

[30] J Thromb Haemost. 2016 Jul; Hyperhomocysteinemia exacerbates Alzheimer's disease pathology by way of the β-amyloid fibrinogen interaction Y. C. Chung et al

Alzheimer's disease sufferers, over 85 years old at death, suggests raised homocysteine may contribute to beta amyloid accumulation and found a clear link between high homocysteine levels and neurofibrillary tangles found in the disease; the effect being most noticeable where there was also evidence of cerebrovascular damage. [31]

Several clinical trials have established links between elevated homocysteine and Alzheimer's disease risk. One study followed up a trial group of 1092 elderly people, who had all been dementia free eight years earlier. In the intervening years, 83 of them developed Alzheimer's disease. Most notably it found that individuals who had the highest homocysteine levels (over 14 µmol/L) at the trial start (baseline), had almost twice the risk of developing Alzheimer's disease. Researchers also found that when plasma homocysteine increased by 5 µmol/litre the risk of developing Alzheimer's disease increased by 40%. [32] Another study found a strong association between higher homocysteine levels and cognitive impairment. Participants in the highest quartile (25%) for homocysteine levels were more than twice as likely to be in the lowest quartile for cognitive test scores compared to those with the lowest homocysteine levels. **[33]**

Elevated homocysteine is also a reflection of dysfunctional methylation. The brain relies on good SAMe supply and post mortem studies have found seriously low concentrations in the brain of Alzheimer's disease sufferers [34] A meta-analysis, which looked at 68 studies found strong links between raised homocysteine and low levels of methylation nutrients folic acid and vitamin B12 and concluded that these factors might also increase the risk of developing Alzheimer's disease. [35]

Conversely, trials which provided high doses of B vitamins to high risk groups showed encouraging results by improving methylation. A two-year trial involving 299 elderly men found that those in the B vitamin treatment group had lower homocysteine levels and a slower rate of increase in circulating beta amyloid, 4.9%, compared to 18.5% in the placebo group. [36]

Another trial aimed to test the effectiveness of folic acid supplementation (800 µg daily) on cognitive function in 818 adults, aged between 50 and 70 years old, who all had high homocysteine levels, but not MCI. Participants in the treatment group experienced a 26% decline in homocysteine levels as well as a significant improvement in cognitive function compared to the placebo group over the 3-year period. [37]

A team at Oxford university have carried out various trials to see whether it is possible to halt brain atrophy in the brain regions related to cognitive decline in Alzheimer's disease by lowering elevated plasma homocysteine using B vitamins.
In their first randomized controlled study on elderly individuals with mild cognitive impairment (MCI) they showed that participants in the B-vitamin treatment group (folic acid 0.8 mg, vitamin B6 20 mg, vitamin B12 0.5 mg daily) experienced a reduced shrinkage of the whole brain volume over 2 years compared to the placebo group. Furthermore, some of those in the treatment group with the highest levels of

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[37] Lancet. 2007 Effect of 3-year folic acid supplementation on cognitive function in older adults in the FACIT trial: a randomised, double blind, controlled trial. (Durga J[1], van Boxtel MP, Schouten EG, Kok FJ, Jolles J, Katan MB, Verhoef P)

homocysteine (over 13 µmol/L) at baseline, experienced atrophy rate reductions as high as 53%. [38] . Participants with the greatest atrophy rates also performed worse in final cognitive tests.
A follow up report giving results from cognitive tests suggested that B vitamins decreased cognitive and clinical deterioration, especially in participants with high baseline homocysteine, above the median (11.3 µmol/L) [39]

A further trial showed that B-vitamin treatment reduced atrophy by seven - fold in the specific grey matter (GM) brain regions which are most vulnerable in the Alzheimer's process. Those in the placebo group, who had higher homocysteine levels at baseline experienced the fastest GM atrophy, while those receiving the B-vitamin treatment, who had high baseline homocysteine levels (above 11 µmol/L) had the least atrophy. Their results indicated that B vitamins can decrease the shrinkage rate in brain regions that are most susceptible to Alzheimer's disease and affected by cognitive impairment. [40].

In further analysis of the above trials they found that those with the highest baseline omega 3 fatty acids levels derived the greatest benefit from taking B vitamins. [41]This is perhaps not surprising because anti-inflammatory omega-3 fatty acids are essential to maintain the structure of certain parts of brain cell membranes and connections between nerves.

Destruction of neurons leads to a decrease in neurotransmitters. Of the three neurotransmitters commonly affected in Alzheimer's disease, (acetylcholine, serotonin, noradrenaline), acetylcholine (from choline) is the one most adversely affected and is vital for cognitive function, especially forming new memories. Acetylcholine may be affected by homocysteine thiolactone, a homocysteine metabolite, which decreases activity of key enzyme activities that regulate the cholinergic system. This effect has been linked to dementia and cerebrovascular disease. [42]

Homocysteine can also overstimulate NMDA receptors leading to excessive glutamate production. Glutamate is another vital neurotransmitter particularly prominent in the brain, which at correct concentrations is vital for learning and memory. Overactivation can lead to excessive calcium production which destroys neurons.

Increasing intake of choline and B vitamins through diet and supplements is very important. Research shows that SAMe supplements can be highly beneficial in the treatment of Alzheimer's disease. By improving methylation SAMe supplements can help support the availability of choline, needed to make acetylcholine and betaine. SAMe supplements can also directly increase glutathione activity, which is severely depleted in the Alzheimer's disease brain. [43]Glutathione is needed to counter oxidative stress caused by elevated homocysteine.

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7. Clinical Depression

There are numerous possible causes of clinical depression, but the condition has been linked to raised homocysteine. If the brain does not receive constant nourishment from B vitamins, especially active folate (5-MTHF), re-methylation of homocysteine to methionine will be impaired, resulting in elevated homocysteine levels and a decrease in SAMe production. [44]

Inefficient SAMe activity leads to inadequate production and availability of mood governing neurotransmitters serotonin, dopamine, adrenaline and noradrenaline. These all require B vitamins for production and are essential to prevent depression. B vitamins are also essential to produce phospholipids and cell receptors. One study which analysed blood and cerebrospinal fluid from severely depressed patients found that those with elevated homocysteine levels also had considerably lower folate, SAMe and dopamine, adrenaline and serotonin metabolite levels in their cerebrospinal fluid. [45]

Elevated homocysteine levels can also disrupt the balance of noradrenaline, serotonin, dopamine and glutamate. Optimal levels of nitric oxide are essential for regulating these neurotransmitters. Elevated homocysteine has been linked to nitric oxide inhibition so reducing homocysteine may improve neurotransmitter balance. [46]

Many studies show a link between depression and high homocysteine. One large study involving 3,752 men over 72 years old, found that higher homocysteine levels increased depression risk. The researchers concluded that lowering homocysteine reduced depression risk by approximately 20%. [47] Another study of 924 men aged between 46 and 64 years, divided into thirds based on their blood homocysteine levels, found that those in the upper third were more than twice as likely to be depressed as those in the lowest third. [48] Another study reported that 45-55% of depression sufferers had high homocysteine levels. [49] .

Several studies found that depression risk is greatly increased with a defective MTHFR gene. In the large male study above, those carrying the MTHFR C677T polymorphism had higher homocysteine levels and were 22% more likely to have depression than those without the variant. [50]. A meta–analysis investigating the link between MTHFR genetic polymorphisms and psychiatric disorders found that there was a 36% increased chance of depression in those with a defective variant compared to normal. They suggested folate supplements may be helpful for treatment and prevention. [51] One study reported that the MTHFR genetic defect may be present in as many as 70% of depressed patients. [52]

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Increased homocysteine levels indicate functional deficiencies of folate and vitamin B12 and both are critical in synthesis of neurotransmitters by remethylating homocysteine back into SAMe. [53]
Numerous studies have investigated the impact of deficiencies on depression risk. 'A study involving 278 depressed patients found that high homocysteine, vitamin B12 deficiency, and to a lesser extent folate deficiency were all related to depressive disorders, [54] while a U.S. study found a strong link between depression and low folate status in an ethnically diverse population group, aged 15-39. [55]Another reported that folate deficiency is relatively common in depressed people and approximately one-third of those are completely deficient. [56] One report noted that patients with low folate levels may suffer longer and more severe depressive episodes and are 6 times less likely to respond to antidepressants. [57]

Many patients experience a limited response to antidepressant medications, but there is evidence that supplementing with folates, particularly in the activated form L-methylfolate, which readily crosses the blood-brain barrier, and SAMe can improve symptoms by supporting methylation, increasing neurotransmission production and decreasing homocysteine. Several trials using L-methylfolate have proved it is an effective addition to prescription antidepressants and well tolerated. [58]One trial found that 40% of the most severely depressed patients who took 5-MTHF plus an antidepressant experienced significant symptom improvement compared to just 16% who took the antidepressant only. [59]They also experienced improvements much faster and were more likely to continue with the therapy.
SAMe possesses anti-depressant properties. [60] Many trials have shown SAMe to be equally good or better than anti-depressants. It also works much faster and has fewer side effects than pharmaceutical anti -depressants. [61] One recent study found that using SAMe and betaine together, both powerful methyl donors, had a greater effect than SAMe alone, when used in addition to anti-depressants. [62]

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8. Recommendations

Any digestive problems which could interfere with absorption of B vitamins should firstly be addressed, such as possible food intolerances, poor gastric acid production or gut dysbiosis.

Dietary intake of B vitamins, choline and betaine should be increased to improve methylation, as well as foods which raise glutathione levels, such as sulphurous cruciferous vegetables, green tea, turmeric and foods rich in vitamin C and E. Alpha lipoic supplements also raise glutathione levels effectively.

Supplementation with activated forms of B vitamins, - 5-MTHF, methylcobalamin, pyridoxyl-5-phosphate (B6) and possibly riboflavin, may be recommended for a limited time, but where serious long-term deficiencies have developed supplementation may need to continue for a longer period to correct deficiencies. If digestion is poor sublingual forms of methylcobalamin, which dissolve under the tongue, are recommended as they are absorbed into the blood supply directly. Supplementing with powerful methyl donor betaine (TMG) helps the body make more SAMe, while also decreasing homocysteine levels very effectively. There are also good combination supplements available which supply all nutrients that support homocysteine metabolism, such as ‘Homocysteine Supreme’. (designs for health).

If high homocysteine levels are suspected a laboratory homocysteine blood test can measure levels. In the UK a home test kit is available from YorkTest. Homocysteine blood levels are a good indicator of folate, vitamin B12 and vitamin B6 status.
Elevated homocysteine or urinary methylmalonic acid (MMA) levels indicate a vitamin B12 deficiency more accurately than blood tests and the Schilling test can measure vitamin B12 absorption. If kidney function is normal then raised MMA levels, together with high homocysteine, probably indicates either a vitamin B12 or combined vitamin B12 and folate deficiency.

If levels do not decrease, despite using homocysteine lowering nutrients, other factors mentioned in Section 3, such as kidney dysfunction and defective gene mutations, may need to be investigated. Genetic profiling tests such as 23andMe are available.

Conclusion
It is evident that the increased oxidative stress and inflammatory responses caused by elevated homocysteine can adversely affect mood and brain health but by improving status of key methylating nutrients significant improvements can be achieved in their prevention and management.