PART 2  Potential secondary benefits

2  Risk reduction of cardiovascular, cancer diseases and of impaired cognitive function

2.1  Cardiovascular disease
Folate and homocysteine ................................................................. 3
Genetic defects ............................................................................. 3
Other determinants of homocysteine ............................................. 3
Homocysteine and cardiovascular disease ................................. 4
Biological plausibility ................................................................. 4

Table 1. Summary of experimental studies of the effect of homocysteine-lowering therapy on measures of vascular disease ................................................................. 5
Serious clinical vascular events ..................................................... 6

Table 2. Trials of homocysteine-lowering vitamin supplements in people with prior cardiovascular disease ................................................................. 6
Dose response relationship ............................................................ 7
Summary and assessment using FSANZ hierarchy of evidence ....... 7

2.2  Cancer disease ................................................................. 8
Folate and Colorectal Cancer Risk ................................................ 8

Table 4. Summary estimates for folate and colorectal cancer from the meta-analysis by Sanjoaquin et al., 2005: ................................................................. 14
Summary and assessment of FSANZ hierarchy of evidence .......... 14
Folate and Breast Cancer Risk ...................................................... 15

Table 5. Studies of association of circulating and dietary folate concentrations with risk of breast cancer ................................................................. 15
Summary and assessment of FSANZ hierarchy of evidence .......... 20

2.3  Cognitive Function ....................................................... 20
Common Types of Dementia and Cognitive Impairment in Australia ................................................................. 20
Types of Dementia - Categorical or Dimensional Diagnosis ....... 21
Risk factors for dementia ............................................................. 22
Are Low Folate and High Homocysteine Levels Risk Factors for Dementia? ................................................................. 22
Cross-Sectional Studies .............................................................. 22
Case Control Studies .............................................................. 22
Authors:

Cardiovascular disease:
Siobhan Hickling, School of Population Health, The University of Western Australia
(Telephone: 6488 7369, email: siobh@cyllene.uwa.edu.au)

Breast cancer:
Dr Elizabeth Milne, Telethon Institute for Child Health Research
(Telephone: 9489 7756, email: lizm@ichr.uwa.edu.au)

Colorectal cancer:
Gina Ambrosini, School of Population Health, The University of Western Australia
(Telephone: 6488 1273, email: ginaa@cyllene.uwa.edu.au)

Cognitive function:
Professor Leon Flicker, Department of Geriatric Medicine, The University of Western Australia
(Telephone: 9224 3992, email: leonflic@cyllene.uwa.edu.au)
2 Risk reduction of cardiovascular, cancer diseases and of impaired cognitive function

2.1 Cardiovascular disease

1. Folate and cardiovascular disease was considered by the Committee on Medical Aspects of Food and Nutrition Policy (COMA) in 2000 (Department of Health 2000) and updated by the Scientific Advisory Committee on Nutrition (SACN) in 2004 (Department of Health 2004). In 2000, COMA concluded that in the absence of more definitive evidence linking folate directly with cardiovascular disease (CVD) it would not be justifiable to advocate dietary fortification with folic acid solely with the aim of reducing the incidence of CVD. Similarly, the SACN concluded that the evidence was insufficient to draw a causal conclusion from the association of folate and CVD. At present there are a number of large randomised controlled trials testing the hypothesis that folate supplementation will reduce cardiovascular events. These trials need to be completed and data submitted for meta-analysis to estimate more reliably and precisely the effects of folate on cardiovascular disease.

2. The following section of this report will summarise the background of folate and cardiovascular disease and update the SACN information with any key references that were not included in the 2004 report and key references that have been published since the SACN report.

Folate and homocysteine

3. Increased intake of folate effectively lowers total plasma homocysteine concentration (tHcy), and low folate status results in elevated tHcy (Homocysteine Lowering Trialists' Collaboration 1998). Maximal tHcy lowering is observed within the range of 0.4-0.8 mg/day (Wald et al. 2001; van Oort et al. 2003).

4. There are a number of other modifiable and non-modifiable factors associated with tHcy.

Genetic defects

5. Deficiencies of the principal enzymes in the metabolism of homocysteine predispose to elevated plasma homocysteine levels. The most common form of genetically raised tHcy results from inheritance of a variant of methylene tetrahydrofolate reductase (MTHFR) gene. The C677T mutation in the gene for MTHFR is common with 10% of the Australian population homozygous for the gene and 40% heterozygous (Van Bockxmeer et al. 1997). It results in a thermolabile form of the enzyme and a higher plasma level of tHcy among homozygote and heterozygotes with low plasma folate (Jacques et al. 1996). The TT polymorphism reduces production of the methyl donor 5-methyl tetrahydrofolate and increases tHcy by about 20% (Engbersen et al. 1995; Frosett et al. 1995; Klerk et al. 2002).

6. Severe deficiency of cystathione beta synthase (CBS) is the classical severe form of homocystinuria (Engbersen et al. 1995). It occurs in only 1 in 100,000 live births and results in an increase in tHcy of up to 40-fold. A vascular event such as stroke or myocardial infarction occurs before the age of 30 in about half of the untreated homozygotes (Mudd et al. 1985).

Other determinants of homocysteine

8. Other causes of increased homocysteine include various disease states such as renal failure, hypothyroidism, diabetes mellitus, severe psoriasis, acute lymphoblastic leukaemia, breast cancer, ovarian cancer and pancreatic cancer (Engbersen et al. 1995; Frostell et al. 1995; Bostom et al. 1999; Hankey et al. 1999; Ganji et al. 2003). Drugs related to homocysteine metabolism are also reported to induce elevated tHcy especially including methotrexate, phenytoin, carbamazepine and thiazide diuretics (Reffsen et al. 1989; Ueland et al. 1989).

9. Plasma levels of homocysteine increase with age (Bree et al. 2001; Ganji et al. 2003), and are higher in males than females (Lussier-Cacan et al. 1996; Ganji et al. 2003). Other lifestyle factors such as smoking (Nygard et al. 1995; Bree et al. 2001; Ganji et al. 2003; Nurk et al. 2004), physical activity (Nygard et al. 1997), consumption of alcohol (Ganji et al. 2003) and coffee (Nygard et al. 1997; Bree et al. 2001; Verhoef et al. 2002) have also been reported to have an effect on tHcy in the general population.

**Homocysteine and cardiovascular disease**

10. The SACN publication reported on two meta-analyses of observational studies concluding that elevated levels of tHcy were a modest independent risk factor for cardiovascular disease in healthy populations (Homocysteine Studies Collaboration 2002); and individuals with the MTHFR C677T polymorphism had a significantly higher risk of coronary heart disease, particularly in individuals with low folate status (Klerk et al. 2002). Another meta-analysis, which combined both the prospective and MTHFR genotype evidence, concluded there was strong evidence for a causal relationship between elevated levels of tHcy and cardiovascular disease (Wald et al. 2002).

11. Since the SACN report another large meta analysis has been published. In the largest meta-analysis to date of studies examining the association between MTHFR and stroke (111 studies), Casas et al (Casas et al. 2005) found that people who are homozygous for the MTHFR C677T polymorphism have a significantly greater mean tHcy (weighted mean difference 1.93 μmol/L 95% CI 1.38-2.47), and risk of stroke (odds ratio 1.26, 1.14-1.40) than people who are homozygous for the wild type (CC). The greater risk of stroke conferred by MTHFR-677TT is in proportion to the difference in tHcy that can be attributed to the polymorphism. Furthermore, the estimate of risk obtained from the meta-analysis of genetic association studies is similar to that obtained from previous meta-analyses of non-genetic observational studies (Homocysteine Studies Collaboration 2002; Klerk et al. 2002; Wald et al. 2002). Because the two types of studies have different sources of error, their consistency supports a causal role for tHcy.

**Biological plausibility**

12. The biological plausibility was summarised in the SACN report. It has been suggested that elevated tHcy may induce endothelial dysfunction Chambers et al., 2000 - a risk factor for cardiovascular disease (Engbersen et al. 1995; Frostell et al. 1995; Chambers et al. 2000; Widlansky et al. 2003). High doses of folic acid (5-10mg/d) have also been shown to improve flow-mediated dilation in coronary artery disease patients (Title et al. 2000; Doshi et al. 2001) and smokers (O’Grady et al. 2002). forearm blood flow,, but not arterial elasticity, in smokers (Mangoni 2002), and volumetric coronary blood flow in hyperhomocysteinemic patients with coronary artery disease (Willems et al. 2002). This effect was shown to be independent of a plasma homocysteine lowering effect (Doshi et al. 2002). Lower doses of folic acid (e.g. 0.4mg/d), which are attainable through the diet, and result in maximal, or near maximal, tHcy reductions have not shown any effect on flow mediated dilation (Pullin et al. 2001).
Experimental studies and randomised controlled trials of the effects of tHcy-lowering and cardiovascular disease

13. Experimental studies and randomised controlled trials indicate that reducing tHcy with folate produces favourable effects on markers of cardiovascular disease (see Table 1).

Table 1. Summary of experimental studies of the effect of homocysteine-lowering therapy on measures of vascular disease

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Intervention</th>
<th>Design</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carotid artery intima thickness</td>
<td>Carotid atherosclerosis; tHcy &gt; 14 μmol/L, n=38</td>
<td>FA + B6 + B12</td>
<td>'before-after' study</td>
<td>vitamin therapy associated with reduction in rate of progression of plaque area</td>
</tr>
<tr>
<td>(Peterson et al. 1998)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Hackam et al. 2000)</td>
<td>Carotid atherosclerosis, n=101</td>
<td>FA + B6 + B12</td>
<td>'before-after' study</td>
<td>vitamin therapy associated with reduction in rate of progression of plaque area</td>
</tr>
<tr>
<td>(Marcucci et al. 2003)</td>
<td>Renal transplant recipients, n=56</td>
<td>FA + B6 + B12</td>
<td>randomised double-blind crossover</td>
<td>vitamin therapy significantly reduced intima-media thickness, significantly increased intima-media thickness in placebo group</td>
</tr>
<tr>
<td>Endothelium-dependent vasodilation of forearm vessels</td>
<td>Healthy volunteers; tHcy &gt; 75th centile, n=17</td>
<td>FA vs placebo</td>
<td>randomised double-blind crossover</td>
<td>folic acid significantly increased endothelium dependent flow</td>
</tr>
<tr>
<td>(Woo et al. 1999)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Bellamy et al. 1999)</td>
<td>Healthy volunteers, tHcy &gt; 13 μmol/L, n=18</td>
<td>FA vs placebo</td>
<td>randomised double-blind crossover</td>
<td>folic acid significantly enhances endothelial dependent vascular function</td>
</tr>
<tr>
<td>(Wilmink et al. 2000)</td>
<td>Healthy volunteers, n=20</td>
<td>FA vs placebo</td>
<td>randomised double-blind crossover</td>
<td>folic acid pre-treatment prevented lipid-induced reduction in endothelial dependent vascular function</td>
</tr>
<tr>
<td>(Pullin et al. 2001)</td>
<td>Healthy volunteers, n=126</td>
<td>FA vs placebo</td>
<td>randomised double-blind crossover</td>
<td>no change in endothelial-dependent FMD</td>
</tr>
<tr>
<td>Exercise electrocardiography</td>
<td>Healthy siblings of patients with premature atherothrombotic disease, n=167</td>
<td>FA + B6 vs placebo</td>
<td>randomised double-blind crossover</td>
<td>folic acid + B6 reduced rate of abnormal exercise ECG</td>
</tr>
<tr>
<td>(Vermuelen et al. 2000; Vermeulen et al. 2004)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coronary artery restenosis and revascularisation</td>
<td>Patients following successful coronary angioplasty, n=553</td>
<td>FA + B6 + B12 vs placebo</td>
<td>randomised double-blind crossover</td>
<td>vitamin therapy reduced rate of coronary restenosis</td>
</tr>
<tr>
<td>(Schnyder, et al., 2002)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Lange et al. 2004)</td>
<td>Patients following successful coronary angioplasty, n=553</td>
<td>FA + B6 vs placebo</td>
<td>randomised double-blind crossover</td>
<td>vitamin therapy had adverse effects on risk of restenosis</td>
</tr>
</tbody>
</table>
coronary stenting  placebo  
n=636

FA = Folic acid, B6 = vitamin B6, B12 = vitamin B12, RCT = randomized controlled trial
FMD = flow mediated dilation

Serious clinical vascular events

14. The first large intervention trial to report on the effects of folate supplementation on serious clinical vascular events was CHAOS-2 (Baker et al. 2002), where 1882 ischemic heart disease patients received either 5mg folic acid or placebo for two years. Despite reducing tHcy concentrations, folic acid supplementation had no significant effect on the composite end-point of either non-fatal myocardial infarction, cardiovascular death or unplanned revascularization (risk ratio 0.97; 95% CI, 0.72-1.29).

15. The VISP trial evaluated the effect of tHcy lowering by folate, vitamin B6 and vitamin B12 on vascular outcome events such as stroke, heart disease and death. After 2 years of follow-up there was a 2μmol/L (smaller than expected) difference in tHcy between the high-dose and low-dose group, but there was no significant difference in the cumulative incidence of recurrent cerebral infarction (RR 1.0 95% CI: 0.8-1.3), in any coronary event (RR 0.9 95% CI: 0.7-1.2) or death (RR 0.9 95% CI: 0.7-1.1) (Toole et al. 2004). Mandatory fortification of foods with folate in North America is likely to have reduced the statistical power of the VISP study. Indeed there was a lower than anticipated rate of recurrent strokes in both study groups which will have lowered the statistical power.

16. The GOES study, a secondary prevention trial comprising 593 patients with coronary heart disease and receiving statin therapy reported no clinical benefit following a 2-year intervention with low dose folate (0.5 mg/day) (Liem et al. 2003). The relative risk for all cause mortality and a composite of vascular events was 1.05 (95% CI, 0.63-1.75). This study was underpowered and the dose of folate used may have been too low to demonstrate any beneficial effect other than tHcy lowering.

17. There are at least eight ongoing clinical trials which are testing the homocysteine hypothesis (see Table 2). A number of these studies (WACS and HOPE-2) were initiated before the introduction of mandatory fortification of foods with folate in the US and Canada and will therefore be underpowered to test the hypothesis they were originally designed for. These trials need to be completed and individual data be submitted for meta-analysis to estimate more reliably and precisely the effect of tHcy lowering on the risk of vascular disease.

Table 2. Trials of homocysteine-lowering vitamin supplements in people with prior cardiovascular disease

<table>
<thead>
<tr>
<th>Trial (Country)</th>
<th>Fortified population (-/+)</th>
<th>Prior disease</th>
<th>Scheduled number to be randomized</th>
<th>Scheduled duration of treatment (years)</th>
<th>Homocysteine-lowering regimen (mg/d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SU.FOL.OM3 (France)</td>
<td>-</td>
<td>CHD</td>
<td>2000</td>
<td>5</td>
<td>Folic acid 0.5  B12 0.02  B6 3</td>
</tr>
<tr>
<td>WENBIT (Norway)</td>
<td>-</td>
<td>CHD</td>
<td>2800</td>
<td>3</td>
<td>0.8 0.4 40</td>
</tr>
<tr>
<td>NORVITE (Norway)</td>
<td>-</td>
<td>CHD</td>
<td>3750</td>
<td>3</td>
<td>0.8 0.4 40</td>
</tr>
<tr>
<td>SEARCH (UK)</td>
<td>-</td>
<td>CHD</td>
<td>12064</td>
<td>5</td>
<td>2.0 1.0</td>
</tr>
<tr>
<td>HOPE-2 (Canada)</td>
<td>+</td>
<td>CHD</td>
<td>5520</td>
<td>5.5</td>
<td>2.5 1.0 50</td>
</tr>
<tr>
<td>WACS (USA)</td>
<td>+</td>
<td>CHD</td>
<td>3500</td>
<td>7</td>
<td>2.5 1.0 50</td>
</tr>
</tbody>
</table>
Dose response relationship

18. Wald et al reviewed eight studies of adult participants (mean age range between 40 and 65 years) that reported the effect of specified doses of folate up to 1 mg/day on serum folate. For every 100 μg/day rise in folate, serum folate increased by about 2.5 μg/L (Wald et al. 2001). More recently van Oort et al conducted a dose response trial of subjects receiving a daily dose of 50, 100, 200, 400, 600 or 800 μg folate /day and reported similar increases in serum folate (van Oort et al. 2003). They calculated the dose response curve for change in tHcy and reported supplementation with folate at 400 μg /day decreased homocysteine by approximately 22%. From the Homocysteine Studies Collaboration a 25% lower than usual tHcy was associated with an 11% (OR, 0.89; 95% CI, 0.83-0.96) lower ischaemic heart disease risk and 19% (OR, 0.81; 95% CI 0.69-0.95) lower stroke risk (The Homocysteine Studies Collaboration).

19. Mandatory fortification with folate in the US at a level of 140 μg/100 g flour is expected to increase the mean intake of folate 70 to 120 μg per day. Even a small increase in intake of folate (as low as 50 to 100 μg /day) is expected to decrease tHcy by approximately 10% and may have a beneficial effect on reducing the incidence of vascular disease (Wald et al. 2001; Wald et al. 2002; van Oort et al. 2003). At the American Heart Association 44th Annual Conference researchers from the Centers for Disease Control estimated that 31,000 stroke-associated deaths and 17,000 deaths related to ischaemic heart disease may have been prevented in the US since mandatory fortification was implemented (Yang et al. 2004).

Summary and assessment using FSANZ hierarchy of evidence

20. The features in favour of a causal relationship between tHcy and CVD are that the meta-analyses of prospective observational and genetic studies do not share the same potential sources of error, but all reported highly significant results consistent with a strong, dose-related, independent and biologically plausible association between increasing tHcy (from low folate status) and increasing risk of CVD. It is unlikely that the agreement of results in the genetic studies and prospective studies is due to confounding as the groupings for the genetic studies arise from a genetic mutation effectively allocated at random. Furthermore, randomised controlled trials indicate that reducing tHcy by means of folate supplementation produces favourable effects on multiple surrogate markers of cardiovascular disease.

21. However, there are several features that do not support a causal relationship. There is inconsistency in the results of epidemiological studies obtained by different methods with smaller associations or no association in studies with more rigorous methodological design. The finding of a stronger association in case-control studies than cohort studies suggests that elevated tHcy may be an acute-phase reactant that rises after the vascular event in response to tissue damage or tissue repair (Dudman 1999). In addition at present there is a lack of reliable evidence from randomised controlled trials that lowering tHcy with folate prevents clinical vascular events such as stroke and heart disease. To conclude, there is probable evidence that increased intake of folate protects against CVD. However the numerous ongoing randomised controlled trials need to be completed and individual data be submitted for meta-analysis before any firm conclusions can be made about a causal relationship between folate and CVD.
2.2 Cancer diseases

Folate and Colorectal Cancer Risk

22. A review of folate and colorectal cancer (CRC) risk was not included in the UK COMA Report (2000). Only findings on folate supplement use and colon cancer from the Nurses' Health Study (Giovannucci et al. 1998) were reported. The 2000 report reiterated the 1998 COMA report's (Health 1998) finding of 'insufficient evidence for any specific links between folate intake and the development of cancer'.

23. Studies on folate and CRC risk included in the SACN report are listed in Table 3 below (rows shaded in grey).

24. It is not clear as to how studies were assessed for inclusion in the SACN report, however it appears that only cohort studies or nested case-control studies were considered. Most of those included are large, reasonably well conducted studies that contribute to the body of evidence regarding dietary folate and CRC, with the exception of two studies (Glynn et al. 1996; Kato et al. 1999) that included a smaller number of cases and questionable sample sizes in their quartile analyses.

25. Most of the studies cited in the SACN report observed a null association between highest level of folate intake and CRC, versus the lowest level intake of folate. However, significant reductions in risk ranging from 18 to 60%, were reported by three major studies. The Nurses' Health Study reported an inverse association between folate intake and colon cancer in women with low methionine intakes (Giovannucci et al. 1998) and those with a family history of colon cancer (Fuchs et al. 2002). The NHANES I Epidemiology Follow Up Study (Su et al. 2001) reported a significantly reduced colon cancer risk for men consuming the highest level of dietary folate. A pooled analysis of the Nurses' Health Study and the Health Professionals' Follow Up Study (Wei et al. 2004) reported significant reductions in colon cancer risk for men and women consuming the highest level of total folate. Only one study (the Iowa Womens' Health Study) reported a significant inverse relationship between serum folate and colorectal cancer (Kato et al. 1999). All of these studies, with the exception of the pooled analysis (Wei et al. 2004), detected a trend in risk reduction across quartiles or quintiles of folate intake or serum folate.

26. To update the UK SACP Report (2004), published studies on dietary and circulating folate and colorectal cancer were identified by searching PubMed using the following MeSH terms: folic acid, folate, colorectal neoplasms, colonic neoplasms, rectal neoplasms. Studies were limited to those conducted on humans and published in English from 1995 onwards. Other original articles were identified by manual searches of reference lists.

27. No new studies suitable for assessing dietary and circulating folate and CRC risk were identified. Some studies cited in the SACN report have since published results stratified according to diet-gene interactions (van Engeland et al. 2003; Chen et al. 2004; Brink et al. 2005), however with the exception of Brink et al., these are not suitable for inclusion in this review. Brink et al., (2005) examined relationships between folate intake and CRC risk according to K-ras tumor mutation
status (and all types combined) in a subsample of the Netherlands Cohort Study (see Table 3, unshaded rows). It should be noted that this analysis utilised considerably fewer cases (430 vs 760 colon; 150 vs 411 rectal) than an earlier analysis on the entire cohort by Konings et al (2002), as the subsample included only those cases and controls for which tumor tissue was available. In the smaller study by Brink et al, no significant relationships between folate intake and colon cancer risk were reported for men (231 cases) or women (199 cases). However, a significant inverse relationship between folate intake and rectal cancer risk was observed in men (99 cases) and conversely; a significantly increased risk of rectal cancer with increasing folate intakes, in women (51 cases). Konings et al., reported similar findings, however the increased rectal cancer risk for women (based on 152 cases) was not statistically significant. Hence, the finding by Brink of an increased rectal cancer risk in women may be due to chance. This study is discussed further in Part 3.

Table 3. Studies of association of circulating and dietary folate concentrations with risk of colorectal cancer

<table>
<thead>
<tr>
<th>Study (Reference)</th>
<th>Study population</th>
<th>Age range (yrs)</th>
<th>Mean Follow Up (yrs)</th>
<th>No of cases</th>
<th>Adjusted relative risk (95% CI)</th>
<th>Trends</th>
<th>Adjusted for</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study (Reference)</td>
<td>Study population</td>
<td>Age range (yrs)</td>
<td>Mean Follow Up (yrs)</td>
<td>No of cases</td>
<td>Adjusted relative risk (95% CI)</td>
<td>Trends</td>
<td>Adjusted for</td>
</tr>
<tr>
<td>-------------------</td>
<td>------------------</td>
<td>----------------</td>
<td>----------------------</td>
<td>-------------</td>
<td>-------------------------------</td>
<td>--------</td>
<td>-------------</td>
</tr>
<tr>
<td>Giovannucci et al., 1998</td>
<td>88,756 women Nurses' Health Study</td>
<td>30-55</td>
<td>15</td>
<td>442 colon cases</td>
<td>0.48 (0.33 to 0.71) for highest vs. lowest quartile of total folate intake (diet &amp; supps) in women whose methionine intake &lt;1.8g/d. 0.29 (0.15 to 0.56) for multivitamin use for 15 or more years compared to nonusers</td>
<td>( p&lt;0.001 )</td>
<td>Age, aspirin use, physical activity, BMI, smoking, family history of CRC, and red meat, fibre, methionine and fibre intake</td>
</tr>
<tr>
<td>Kato et al., 1999</td>
<td>NCC, 15,785 women Women's Health Study</td>
<td>Mean 62</td>
<td>3-9</td>
<td>108 colon and rectal cases</td>
<td>0.50 (0.26 to 0.95) for highest vs. lowest quartile of serum folate concentrations for CRC. 0.88 (0.46-1.69) for highest vs. lowest quartile of total folate intake (diet &amp; supps) for CRC</td>
<td>( p&lt;0.04 )</td>
<td>Education, race, religion, physical activity, aspirin use, family, alcohol, smoking, energy, macronutrient, fibre, vitamin A, C and E intake, Quetelet Index</td>
</tr>
<tr>
<td>St et al., 2001</td>
<td>10,185 general population MELANESI Epidemiology Follow-up Study</td>
<td>25-74</td>
<td>20</td>
<td>219 colon cases</td>
<td>0.40 (0.28 to 0.88) for highest vs. lowest quartile of dietary folate intake in men. 0.74 (0.35 to 1.61) for highest vs. lowest quartile of dietary folate intake in women with family history of colon cancer in 0.81 (0.32 to 2.07) for highest vs. lowest quartile of dietary folate intake in women with no family history of colon cancer</td>
<td>( p=0.03 )</td>
<td>Age, race, gender, smoking, BMI, family history of colon cancer, intake of red fibre, calcium, vitamin B6, vitamin B12, total energy and alcohol</td>
</tr>
<tr>
<td>Fuchs et al., 2002</td>
<td>88,758 women Nurses' Health Study</td>
<td>30-55</td>
<td>16</td>
<td>538 colon cases</td>
<td>0.48 (0.24 to 0.93) for highest vs. lowest quartile of total folate intake (diet &amp; supps) in women with a family history of colon cancer. 0.81 (0.32 to 2.07) for highest vs. lowest quartile of total folate intake in women with no family history of colon cancer</td>
<td>( p=0.04 )</td>
<td>Age, appendix use, physical activity, BMI, smoking, family history of CRC, age at menopause, alcohol, red meat, alcohol, animal fat, vitamins A, C, D, E, methionine and fibre intake</td>
</tr>
<tr>
<td>Konings et al., 2002</td>
<td>NCC, 120,852 general Netherlands Cohort Study</td>
<td>55-69</td>
<td>7.3</td>
<td>760 colon cases, 411 rectal cases, 5123 non cases</td>
<td>0.73 (0.46 to 1.17) for highest vs. lowest quintile of dietary folate intake for colon cancer in men. 0.68 (0.39 to 1.20) for highest vs. lowest quintile of dietary folate intake for colon cancer in women. 0.66 (0.35 to 1.21) for highest vs. lowest quintile of dietary folate intake for colon cancer in men.</td>
<td>( p=0.03 )</td>
<td>Age, energy intake, family history, alcohol, vitamin C, iron and dietary fibre intake</td>
</tr>
<tr>
<td>Study (Reference)</td>
<td>Study population</td>
<td>Age range (yrs)</td>
<td>Mean Follow Up (yrs)</td>
<td>No of cases</td>
<td>Adjusted relative risk (95% CI)</td>
<td>Trends</td>
<td>Adjusted for</td>
</tr>
<tr>
<td>-------------------</td>
<td>------------------</td>
<td>----------------</td>
<td>----------------------</td>
<td>-------------</td>
<td>--------------------------------</td>
<td>--------</td>
<td>--------------</td>
</tr>
<tr>
<td>(Levi et al. 2000)</td>
<td>CC Hospital, Switzerland</td>
<td>27-74</td>
<td></td>
<td>223 colon and rectal 491 controls</td>
<td>1.54 (0.8-3.1) for highest vs lowest tertile of dietary folate for colorectal cancer</td>
<td>NS</td>
<td>Age, gender, education, smoking, alcohol, BMI, total energy and fiber, physical activity</td>
</tr>
<tr>
<td>(Slattery et al. 1997)</td>
<td>CC Multi-centre populations, USA</td>
<td>30-79</td>
<td></td>
<td>1993 colon 2410 controls</td>
<td>1.2 (0.8-1.6) for highest vs lowest quintile of dietary folate intake for colon cancer in men 0.9 (0.6-1.3) for highest vs lowest quintile of dietary folate intake for colon cancer in women</td>
<td>p=0.70</td>
<td>Age, BMI, physical activity, aspirin use, family history, total energy and calcium intake</td>
</tr>
<tr>
<td>(Boutron-Ruault et al. 1996)</td>
<td>Hospital CC Burgundy, France</td>
<td>30-79</td>
<td></td>
<td>106 colon 65 rectal 309 controls</td>
<td>1.0 (0.5-2.0) for highest vs lowest tertile of dietary folate intake for colorectal cancer</td>
<td>p=0.95</td>
<td>Caloric intake, age, sex, BMI, alcohol, vitamin B6</td>
</tr>
<tr>
<td>(Ma et al. 1997)</td>
<td>NCC, males Physicians' Health Study</td>
<td>40-84</td>
<td></td>
<td>202 colorectal 326 controls</td>
<td>1.78 (0.93-3.42) for plasma folate &lt; 3ng/mL (deficient folate level) vs plasma folate 3ng/mL (adequate folate level) for colorectal cancer.</td>
<td>NS</td>
<td>Age, smoking, alcohol, multivitamin use, BMI, physical activity, aspirin use</td>
</tr>
<tr>
<td>(La Vecchia et al. 2002)</td>
<td>CC Hospitals in 6 regions of Italy</td>
<td>20-74</td>
<td></td>
<td>1225 colon 728 rectal</td>
<td>0.65 (0.50-0.85) for highest vs lowest quintile of dietary folate intake for CRC</td>
<td>p&lt;0.01</td>
<td>Age, SES, gender, smoking, alcohol, BMI, physical activity, family</td>
</tr>
<tr>
<td>Study (Reference)</td>
<td>Study population</td>
<td>Age range (yrs)</td>
<td>Mean Follow Up (yrs)</td>
<td>No of cases</td>
<td>Adjusted relative risk (95% CI)</td>
<td>Trends</td>
<td>Adjusted for</td>
</tr>
<tr>
<td>------------------</td>
<td>------------------</td>
<td>-----------------</td>
<td>----------------------</td>
<td>-------------</td>
<td>--------------------------------</td>
<td>--------</td>
<td>-------------</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>4154</td>
<td>in men 0.70 (0.53-0.93) for highest vs lowest quintile of dietary folate intake for CRC in women 0.81 (0.66-1.01) for highest vs lowest quintile of dietary folate intake for colon cancer (sexes comb.) 0.59 (0.45-0.77) for highest vs lowest quintile of dietary folate intake for rectal cancer (sexes comb.)</td>
<td>p&lt;0.01</td>
<td>history, total energy and fiber intakes</td>
</tr>
<tr>
<td>(Brink et al. 2005)</td>
<td>Netherlands Cohort Study (NCC)</td>
<td>Mean 61</td>
<td>7.3</td>
<td>448 colon 160 rectal</td>
<td>0.87 (0.66-1.14) for 100mg/day increase in folate intake for colon cancer in men 0.98 (0.62-1.56) for 100mg/day increase in folate intake for colon cancer in women 0.58 (0.36-0.93) for 100mg/day increase in folate intake for rectal cancer in men 1.85 (1.13-3.02) for 100mg/day increase in folate intake for rectal cancer in women</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>(Le Marchand et al. 2002)</td>
<td>CC</td>
<td>57-74</td>
<td>727 colon and rectal</td>
<td>0.9 (0.6-1.3) for highest vs lowest quartile of dietary folate for colorectal cancer</td>
<td>p=0.43</td>
<td>Age, gender, ethnicity, smoking, alcohol, education, aspirin use, physical activity, family history, BMI, total energy and non starch polysaccharide intake from veg, calcium from food and supplements</td>
<td></td>
</tr>
</tbody>
</table>

_NCC nested case control study; CC case control study; BMI, body mass index; NSAID, non-steroidal anti-inflammatory drugs; NS, not stated._

28. Five case-control studies (Boutron-Ruault et al. 1996; Slattery et al. 1997; Levi et al. 2000; La Vecchia et al. 2002; Le Marchand et al. 2002) and a nested case-control study (Ma et al. 1997) not included in the SACN report were identified. These are shown in Table 3 in unshaded rows. Inclusion of two of these studies is questionable owing to poor response rates (Boutron-Ruault et al. 1996; Le Marchand et al. 2002) and a modest sample size (Boutron-Ruault et al. 1996). Only La Vecchia et al reported a significant inverse association between folate intake, colorectal cancer and rectal cancer, with trends in risk reduction across quintiles of folate intake. The remainder
reported null findings.

29. A meta-analysis of folate intake and CRC risk was published in early 2005 (Sanjoaquin et al. 2005). This included all of the studies in Table 3 that presented results as relative risks or odds ratios comparing the highest quartile or quintile of folate intake to the lowest, i.e., all studies except Ma et al and Fuchs et al (Ma et al. 1997; Fuchs et al. 2002) also included one study published before 1995 (Freudenheim et al. 1991).

30. Results of the meta-analyses are shown in Table 4. No significant heterogeneity was found between cohort studies, and the summary estimate of CRC risk in cohort studies indicated a 25% reduction in risk for the highest quintile of dietary folate. There was significant heterogeneity between case-control studies reporting dietary folate intake and CRC risk. Meta-regression analysis indicated that within cohort studies, the inverse relationship between dietary folate and risk (Table 4) was stronger for colon than rectal cancer (p=0.03), and marginally stronger than total folate (p=0.06), but was the same for men and women. Among case-control studies, the estimated effects were similar for men and women, type of cancer and source of folate.

Table 4. Summary estimates for folate and colorectal cancer from the meta-analysis by Sanjoaquin et al., 2005:

<table>
<thead>
<tr>
<th>Summary Estimate of Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cohort Studies</strong></td>
</tr>
<tr>
<td>---------------------</td>
</tr>
<tr>
<td>Highest quintile of folate intake vs lowest quintile</td>
</tr>
<tr>
<td>Case-Control Studies</td>
</tr>
<tr>
<td>Lowest quintile</td>
</tr>
<tr>
<td>Highest quartile of folate intake vs lowest quartile</td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>

31. The MTHFR polymorphism (C677T) correlates with reduced MTHFR activity, resulting in reduced plasma folate and increased plasma homocysteine (Ma et al. 1997). This leads to the reasonable deduction that 677TT may be a risk factor of colorectal cancer. However the Health Professionals' Follow Up Study (Chen et al. 1996), the Physicians' Health Study (Ma et al. 1997) and a large, multi-centred US case-control study (Slattery et al. 1999) have reported significantly reduced colorectal cancer risks in homozygotes for this polymorphism (677TT) compared to either wild type (677CC) or heterozygotes (677CT) and wild type combined.

32. As mentioned in the SACN report, low folate intake coupled with high alcohol consumption has been associated with a higher risk of colon cancer (Giovannucci et al. 1995; Glynn et al. 1996; Giovannucci et al. 1998; Su et al. 2001). In addition, La Vecchia et al, 2002 found a lower risk of CRC in women with high folate and low alcohol intakes. A few studies have examined interactions between the MTHFR-C677T polymorphism, methyl-poor diets (high alcohol-low folate diets) and CRC. The protective effect of homozygosity for MTHRF-677TT seems to be lost when the diet is high in alcohol and low in folate (Chen et al. 1996; Ma et al. 1997), however this requires confirmation with further research.

**Summary and assessment of FSANZ hierarchy of evidence**

33. Eighteen published papers were reviewed for this report of which, six reported significant inverse
relationships between dietary or serum folate and CRC, plus trends in risk reduction across increasing levels of folate intake or serum folate (Giovannucci et al. 1998; Kato et al. 1999; Su et al. 2001; Fuchs et al. 2002; La Vecchia et al. 2002; Wei et al. 2004). It is important to note that three of these significant studies (Giovannucci et al. 1998; Fuchs et al. 2002; Wei et al. 2004) are based on data from the very large Nurses' Health Study. Of these, Wei et al (2004) (Wei et al. 2004) reports on extended follow up and a pooled analysis of the Nurses' Health Study and the Health Professionals' Follow-Up Study. The Nurses' Health Study was previously reported on by Giovannucci et al (1995 and 1998) (Giovannucci et al. 1995; Giovannucci et al. 1998) and Fuchs et al (2002)(Fuchs et al. 2002). The Nurses' Health Study is a cohort of 88,756 women. This indicates that many of the reviewed studies may have been underpowered to detect a significant relationship between dietary or circulating folate and CRC risk. The misclassification of folate intakes is also likely to have contributed to a lack of detectable differences.

34. One new study on a cohort subsample reported a significantly increased risk of rectal cancer in women with increasing folate intakes (Brink et al. 2005), however this is not supported by an analysis of the entire cohort (Konings et al. 2002), which indicates that this may be a chance finding due to a smaller sample size. Wei et al (2004) reported a non-significant increase in risk for rectal cancer in women. As the majority of studies report either colon cancer risk or colorectal cancer risk combined, it is not possible at this stage to make a thorough assessment of whether folate intake is protective against rectal cancer or not, particularly in women.

35. The recently published meta-analysis of CRC supports a protective effect from increased folate intakes, and a stronger inverse relationship between folate intake and colon cancer, specifically (Sanjoaquin et al. 2005). Only one (La Vecchia et al. 2002) of the seventeen studies reviewed reported a significant protective effect from increased folate intake on rectal cancer.

36. No randomised controlled trials have been published, and most of the published results are based on cohort studies.

37. This review, coupled with findings of the meta-analysis, concludes that there is:

- probable evidence that increasing folic acid intake could reduce the risk of colon cancer, and
- insufficient evidence that increasing folic acid intake could reduce the risk of rectal cancer.

Folate and Breast Cancer Risk

38. The 2000 COMA report concluded that there was insufficient evidence for any specific links between folate intake and the development of cancer. There was no discussion of a possible association between folic acid intake and breast cancer risk.

39. The 2004 SACN report considered the folic acid - breast cancer association. Table 5 shows details of the studies identified in the 2004 report (rows shaded in grey); studies published since the SACN report (or otherwise not included in it) are presented in the unshaded rows.

40. To update the UK SACN Report (2004), published studies on folate and breast cancer were identified by searching PubMed using the following MeSH terms; folic acid, folate, breast neoplasms. Studies were limited to those conducted on humans and published in English from 1995 onwards. Other original studies were identified in review articles.

Table 5. Studies of association of circulating and dietary folate concentrations with risk of breast cancer

15
<table>
<thead>
<tr>
<th>Study Reference</th>
<th>Study population</th>
<th>Age range (yrs)</th>
<th>Mean follow-up (yrs)</th>
<th>No of cases</th>
<th>Adjusted relative risk (95% CI)</th>
<th>Trends</th>
<th>Adjusted for</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment</td>
<td>Dietary Folic Acid</td>
<td>Folic Acid Status</td>
<td>Folic Acid Level</td>
<td>Outcome</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-----------</td>
<td>-------------------</td>
<td>------------------</td>
<td>-----------------</td>
<td>---------</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>Low</td>
<td>50%</td>
<td>50 ppm</td>
<td>NS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>B</td>
<td>High</td>
<td>75%</td>
<td>75 ppm</td>
<td>NS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>Medium</td>
<td>60%</td>
<td>60 ppm</td>
<td>NS</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Note:**
- NS: Not Significant
- Dietary Folic Acid: Indicates the level of folic acid intake through diet.
- Folic Acid Status: Represents the percentage of folic acid status.
- Folic Acid Level: Shows the concentration of folic acid.
- Outcome: Indicates the result of the study.
<table>
<thead>
<tr>
<th>(Sellers et al. 2002)</th>
<th>34,393 Iowa Women’s Health Study</th>
<th>55-69</th>
<th>14</th>
<th>1,875</th>
<th>1.43 (1.02 to 2.02) for lowest 10th percentile of dietary folate intake and &gt; 4g alcohol intake per day vs. non-drinkers above the 50th percentile of dietary folate intake 2.10 (1.18-3.85) for lowest 10th percentile of dietary folate intake and &gt; 4g alcohol intake per day vs. non-drinkers above the 50th percentile of dietary folate intake for women with oestrogen receptor negative tumours.</th>
<th>Age, energy intake, methionone intake, education, age at menarche, age at menopause, oral contraceptive use, HRT, parity, age at first birth, BMI, waist-to-hip ratio, height, smoking and physical activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Cho et al. 2003)</td>
<td>90,655 Nurses’ Health Study II</td>
<td>26-46</td>
<td>8</td>
<td>714</td>
<td>1.03 (0.81-1.32) for highest vs. lowest quintile of folate intake</td>
<td>p=0.95 Age, total energy intake, parity, age at first birth, family history of breast cancer/disease, OCP use, alcohol intake, smoking, BMI, weight gain/loss, age at menarche, height</td>
</tr>
<tr>
<td>(Beilby et al. 2004)</td>
<td>CC Western Australia</td>
<td>30-84</td>
<td>-</td>
<td>141</td>
<td>0.23 (0.09-0.54) for highest vs. lowest quartile of serum folate concentration</td>
<td>p=0.00 1 Age at menarche, parity, alcohol and fat intake, MTHFR C677T genotype.</td>
</tr>
<tr>
<td>(Shrubsole et al. 2004)</td>
<td>CC China</td>
<td>25-64</td>
<td>-</td>
<td>1144</td>
<td>ORs all ~ 0.5 for highest vs lowest quartile of folate intake; ORs vary slightly by MTHFR genotype.</td>
<td>Overall p &lt; 0.05 Age, age at first birth, waist-to-hip ratio, energy intake, meat, physical activity, B6, B12 &amp; methionone intake</td>
</tr>
<tr>
<td>(Chen et al. 2005)</td>
<td>CC New York</td>
<td>NS</td>
<td>-</td>
<td>1481</td>
<td>0.61 (0.41-0.93) for highest vs. lowest quintile of dietary folate intake (only in women who did not use supplements)</td>
<td>p=0.06 Age, total energy intake, family history of breast cancer/disease, BMI</td>
</tr>
<tr>
<td>(Hussien et al. 2005)</td>
<td>Cross-sectional N Ireland</td>
<td>NS</td>
<td>-</td>
<td>64</td>
<td>Non-significant difference in mean red cell folate between breast cancer cases and benign breast disease controls</td>
<td>NS Crude analysis only.</td>
</tr>
</tbody>
</table>

HRT, hormone replacement therapy; BMI, body mass index; NS, not stated; NCC, nested case-control; MC, matched control, CC, case-
41. The 2004 SACN report included the assessment of evidence from prospective studies – including cohort and nested case-control studies – only. The reasons for this were not given, but it should be noted that between 1995 and 2003, seven case-control studies (Freudenheim et al. 1996; Thorand et al. 1998; Potischman et al. 1999; Negri et al. 2000; Rohan et al. 2000; Levi et al. 2001; Adzesen 2003) and a case-cohort study (Rohan et al. 2000) on the effect of folate on breast cancer risk were published. Two of these studies (Thorand et al. 1998; Potischman et al. 1999) found no association, while three studies found an overall protective effect (Freudenheim et al. 1996; Ronco et al. 1999; Adzesen 2003) and three found a protective effect particularly among alcohol drinkers (Negri et al. 2000; Rohan et al. 2000; Levi et al. 2001). These studies have not been added to Table 5.

42. Of the prospective studies of folate intake and breast cancer identified in the 2004 SACN report, two reported null results (Wu et al. 1999; Feigelson et al. 2003), while three reported a protective effect of folate in alcohol drinkers only (Zhang et al. 1999; Sellers et al. 2001; Zhang et al. 2003). The other study reported a protective effect among women with a family history of breast cancer and in women who drink alcohol.* As discussed in the SACN report, alcohol has been shown to act as a folate (or methyl group) antagonist (Halsted et al. 2002). Thus, it is biologically plausible that folate could protect against breast cancer in women at higher risk because of their alcohol intake.

43. Two prospective studies published prior to the SACN report were not included in that report: one from the Iowa Women’s Health Study (Sellers et al. 2002) and one from the Nurses’ Health Cohort II (Cho et al. 2003). The details and a summary of results from these two studies have been added to Table 5. Briefly, the latter study reported no association, while the study by Sellers et al. reported an increased risk of breast cancer in women with low folate and high alcohol intake, particularly if they have an oestrogen receptor negative tumour. Note that the table now includes three studies from the Iowa Women’s Health Study (by Sellers et al.), which examine various subgroups within the same cohort. The lack of independence of the results of these studies must be taken into account when assessing the weight of evidence.

44. Four studies have been published on the association between folate intake and breast cancer since the SACN report; details of these studies have been added to Table 5 (unshaded rows). These include three case-controls studies (Beilby et al. 2004; Shrubsole et al. 2004; Chen et al. 2005) and a cross-sectional study (Hussien et al. 2005). The study by Shrubsole et al. (Shrubsole et al. 2004) reported a protective effect of folate in a Chinese population of non-users of alcohol. The Australian study (Beilby et al. 2004) also reported a protective effect, but the response among controls was poor, making it difficult to assess the level of bias introduced by likely differences in distribution of SES and other relevant lifestyle factors among cases and controls. The third case-control study found a protective effect only among non-users of supplements, but did not adjust for alcohol consumption even though it was noted that subjects’ provision of a blood sample was related to use of alcohol (Chen et al. 2005). The cross-sectional study compared red cell folate levels among women with breast cancer and women with benign breast disease (Hussien et al. 2005). The analysis was unadjusted, and the difference in geometric means was non-significant.

45. As mentioned in the SACN report, it has been suggested that the MTHFR C677T polymorphism may modify the association between the folate intake and risk of breast cancer, because of its crucial role in the folate metabolic pathway. Accordingly, the most recent studies have examined this putative gene-environment interaction (Beilby et al. 2004; Le Marchand et al. 2004; Shrubsole

* This category added to Table 5 for current report (Sellers et al., 2004).
et al. 2004; Chen et al. 2005). The latter two studies provide some evidence that high folate intake may be more protective in women with the homozygous polymorphism (677TT), while the other two studies show no interactive effects. Further research is required before any firm conclusions can be drawn.

Summary and assessment of FSANZ hierarchy of evidence

46. Since 1995, 20 epidemiological studies have been published on the association between folate intake and risk of breast cancer. Of the eight prospective studies, three were null and five reported a protective effect of folate only among women in higher strata of alcohol intake. Of the remaining 12 studies, two were null, three reported a protective effect of folate only among women in higher strata of alcohol intake, and seven reported an overall protective effect.

47. After taking account of the quality of data provided by these studies, we conclude that there is possible evidence that high levels of folate intake protect against breast cancer, particularly among women at greater risk because of higher alcohol consumption.

2.3 Cognitive Function

48. Dementia is a common disabling condition of older people. The Australian Institute of Health and Welfare report has estimated that this condition is the second leading cause of years of life lost due to disability. It is the sixth major causes of disability-adjusted-life-years lost in Australia, and on this measure are ranked ahead of asthma and diabetes mellitus (Van Der Weyden 1999- REF). Because of the ageing of the Australian population there is almost certainly going to be a dramatic increase in the numbers affected such that by 2050 the number of people with dementia will rise to over 700,000 (Economics. February 2005).

49. Dementia is a syndrome due to disease of the brain in which there is a disturbance of multiple higher cortical functions including memory and other cognitive processes. For the syndrome of cognitive decline to fulfil the criteria for dementia, this decline must be severe enough to impair personal activities of daily living, and, for a confident clinical diagnosis, this impairment should have been evident for at least six months (Henderson et al. January 1998). The prevalence of dementia in older people doubles for every 5.1 years of age (Jorm et al. 1987). Three meta-analyses all point to the prevalence rising from approximately 1% in the age group 60 to 64 years to 25% in the age group 85+ years (Henderson et al. January 1998).

50. The entity of ‘cognitive impairment not dementia’ is more common than dementing processes (16.8% versus 8%), but it is not as clearly associated with burden to the affected individuals and their carers (Graham et al. 1997). The specific conditions identified within this category of cognitive impairment included delirium, alcohol use, drug intoxication, depression, psychiatric disease, memory impairment associated with the ageing process and mental retardation. Nevertheless, the general conclusion is that the problems of cognitive health in old age extend beyond the issue of dementia.

Common Types of Dementia and Cognitive Impairment in Australia

51. The mixture of types of dementia varies in different societies. In Australia, Alzheimer’s disease (AD) is the predominant form of dementia, although vascular dementia (VD) is also common, both by itself and in conjunction with other causes of dementia. Waite et al., (Waite et al. 1997) found that among a group of community-dwelling elderly people in Sydney 43% of the individuals with dementia had AD, 13% had AD in combination with another disease, another 13% had VD, and 11% had VD mixed with another type of dementia. In patients attending a Memory Clinic in Melbourne, 68% were thought to have AD and 28% vascular dementia (Ames et al. 1992). In a
Sydney Memory Clinic 73% were thought to have AD, with 15% having VD and 8% having a combination of AD and VD (Brodat 1990). An autopsy study in Western Australia found that 45% of patients with dementia had AD, and another 28% had AD with another brain disease (Ojeda et al. 1986). Although AD is the commonest cause of dementia in Australia, VD may be the major cause of dementia in Japanese and Chinese residents (Jorm 1991). It is now clear that dementia associated with Lewy Bodies, is also common, that it can be reliably distinguished clinically from AD and that it may account for over 10% of all cases of dementia.

52. The transitional state between normal ageing and mild dementia has been classified by different titles and methodologies. The most recent, popular addition has been mild cognitive impairment (MCI). Originally described by Petersen et al. (Petersen 1999), criteria included:

- A concern about the patient’s memory, expressed by either the patient, their family, or the patient’s physician
- Normal activities of daily living
- Normal general cognitive function
- Abnormal memory for age, or other specific cognitive domain (Petersen 2001)
- Not demented

53. One of the major reasons given for development of this nosological entity was so as to be able to efficiently identify older people who were at greater risk for the development of dementia and thus allow the examination of interventions which may prevent the development of dementia. It is apparent that clinic based populations are more likely to demonstrate higher conversion rates to dementia than those studies which used population based sampling techniques. A systematic review (Bruscoli 2004) which examined 19 studies reported between 1991 and 2001, found that the conversion rate for clinic attendees was twice that of community living volunteers, 15% versus 7.5% respectively. Given that community volunteers are self selected, the true rate for general community subjects may even be lower.

54. Although the purpose of identification of MCI was to allow testing of dementia prevention strategies, no such interventions have been successfully identified. As dementia is a major health issue for older people, the eventual targeting of such interventions only for older people with MCI, would suggest that these strategies would have to be either costly, or marred by side effects, because otherwise a universal public health approach would be indicated. Also, the prospects of harming older people are significant, by labeling them with a diagnostic entity, with as yet no proven interventions. This labeling may precipitate adverse psychological consequences as well as raising medico-legal issues such as casting doubt on their capacity to perform complex functional activities, e.g. driving. There is, as yet, no consensus on how to operationalise the criteria to maximize the validity as a dementia pre-syndrome.

**Types of Dementia - Categorical or Dimensional Diagnosis**

55. Until recently there have been considered to be two major forms of dementia - AD and VD. It is now understood that, in older people, these diagnoses are by no means clear cut. In a representative sample of 85 year olds in Sweden, infarcts were more common in people with dementia than people with normal cognition and there were more subjects with VD than with AD (Skoog et al. 1993). Many people with dementia have some elements of both AD and VD. Those who have strokes are more likely to develop dementia if they have Alzheimer pathology before the stroke, and many people with AD also have damage due to disease of small vessels, which appears on neuro-imaging as microinfarctions in the white matter (leukoariosis). The presence of cerebral atrophy also predicts the risk of dementia following lacunar infarction (Loeb et al. 1992). Certainly the two
common types of dementia are not mutually exclusive; patients may have either predominantly Alzheimer pathology with some vascular damage, or predominantly vascular dementia with some evidence of Alzheimer pathology. This is hardly surprising as both processes are associated with advancing age, and older individuals are therefore clearly at risk for both cerebrovascular disease and AD. Indeed, vascular damage may be predisposed by Alzheimer type pathology.

56. Ageing is the most important risk factor for AD. As individuals age, some cognitive abilities decline (Laursen 1997- REF). This is particularly marked for tasks involving reaction time and memory processing. It is unclear whether these changes form a continuum with the clinical presentation of people with AD. Cerebral microinfarcts are also a frequent accompaniment of ageing. Whether these microinfarcts produce significant cognitive impairment is debatable. AD and VD may share other risk factors in addition to ageing such as systolic blood pressure. Raised midlife systolic BP has been shown to be associated with cognitive decline, decreased brain volume, and increased white matter hyperintensities. Risk factors that are common to both conditions and that are remediable are obvious targets for the development of preventive strategies.

Risk factors for dementia

57. Proven risk factors for AD include ageing, family history of AD, Down syndrome and the E4 genotype of apolipoprotein E. Taken together, the known genetic mutations account for less than 5% of all cases. The presence of the E4 allele of the apolipoprotein E (apoE), on the other hand, has been associated with the common sporadic and late-onset dementias (Anonymous. 1996). Other possible risk factors include head trauma, exposure to aluminium, history of depression, fingerprint patterns, hypothyroidism, occupational exposure to electromagnetic radiation, lack of physical activity, poor educational achievement, lack of ongoing intellectual or social stimulation, obesity, lack of moderate alcohol intake, hypertension, diabetes mellitus and smoking. Risk factors for VD include old age, hypertension, family history, diabetes mellitus, hypercholesterolaemia and smoking.

Are Low Folate and High Homocysteine Levels Risk Factors for Dementia?

58. There is some experimental work that hyperhomocysteinemia actually produces cognitive dysfunction. For example, rats treated with parenteral homocysteine for 3 weeks early in life still demonstrated poor cognitive function in experimental tasks at the age of 60 days (Engbersen et al. 1995; Frosst et al. 1995; Streck et al. 2004). Published human studies identified by PubMed searches using the following MESH terms, folate folic acid, homocysteine, cognition, cognitive disorders and dementia, English language from 1995.

Cross-Sectional Studies

59. Initially, an inverse correlation was found between spatial copying skills and Hcy in 68 subjects (Riggs et al. 1996). Another group reported elevated Hcy levels in a general psychogeriatric population, affecting both demented and non-demented patients, the latter group mainly suffering from depression (Nilsson et al. 1996). Since then there have been numerous studies. Studies that have found an association for high Hcy or low folate with dementia and cognitive impairment include (Prins et al. 2002; Miller et al. 2003; Naggia et al. 2003; Sachdev et al. 2003; Almeida et al. 2004; Engelborghs et al. 2004; Garcia et al. 2004; Quadri et al. 2004; Ravaglia et al. 2004; Wright et al. 2004; Adunksy 2005; Aleman et al. 2005; Schafer et al. 2005). Studies that have failed to find a statistically significant association include Ariogul (Ariogul et al. 2005), Bunce et al (Teunissen et al. 2003; Bunce et al. 2004). Teunissen et al (Teunissen et al. 2003) and Bunce et al.(Bunce et al. 2004; Ariogul et al. 2005; Bunce et al. 2005)

Case Control Studies
60. In a small case-control study (50 subjects per group) (Joosten et al. 1997) demonstrated significant differences in Hcy in AD patients compared to hospital controls despite the hospital controls having a large number of patients with vascular disease. Similarly, another small case-control study (30 subjects per group) (McCaddon et al. 1998) demonstrated significant differences between AD patients and community controls in B12, folate and HC. In the landmark optimally designed case-control study (Clarke et al. 1998) showed that serum Hcy levels were significantly higher, and folate and B12 lower, in patients with dementia of Alzheimer’s type and in patients with confirmed AD. The odds ratio of confirmed AD associated with a HC level in the top tertile compared with bottom tertile was 4.5 [95% CI: 2.2, 9.2]. Similar calculations yielded an odds ratio (OR) of 3.3 [1.8, 6.3] for serum folate and an odds ratio of 4.3 [2.1, 8.8] for serum B12. The lack of a relationship with duration of symptoms argues against this being a consequence of poor nutrition secondary to disordered eating habits with increasing cognitive impairment. These small positive studies contrast with the nested case-control studies from the Rotterdam Study (Kalmijn et al. 1999).

Although there appeared to be an initial negative correlation between baseline cognitive score (MMSE) and homocysteine, OR for highest versus lowest tertile 1.7 [0.70, 4.15], this was not present after adjustment for age, sex and education. Having defined those people with cognitive decline as having more than 1 point annual decline on MMSE, there was no apparent difference between those subjects who declined and the controls, although the subjects with greater cognitive impairment were more likely to be lost to follow-up.

61. Since then five case control studies have found an inverse association between elevated levels of Hcy and cognitive impairment or dementia (McIlroy et al. 2002; McCaddon et al. 2003; Religa et al. 2003; Mizrahi et al. 2004; Ravaglia et al. 2004). The one study with a statistically non-significant association was small, 43 AD patients and 37 control subjects (Miller et al. 2002). The odds ratio in that study for elevated plasma Hcy was 2.2 (95% CI; 0.31, 16)

**Cohort Studies**

62. The arguments for reverse causality in this area are very strong, ie that as older people become more cognitively impaired their eating habits may alter, their general nutrition may deteriorate and this may specifically affect micronutrients. For this reason cohort studies of normal older subjects with extended periods of follow-up from baseline assessment are desirable. The question of whether Hcy levels “track” i.e. baseline levels correlate strongly with follow-up levels is unclear. A summary of the available cohort studies is presented in Table 6.

63. These data suggest an increased risk of accelerated cognitive impairment, leading to dementia and AD. The data that are available suggest that this is independent of obvious vascular damage to the brain, eg in the study by (Dufouil et al. 2003) adjusting for number of white matter intensities seen on magnetic resonance imaging (a marker of vascular damage to the brain) did not substantially alter the effect of Hcy.

**Randomised Trials and Systematic Reviews**

64. A systematic review has been performed summarizing the four available randomised controlled trials of folate. One trial enrolled healthy women, and the other three recruited people with mild to moderate cognitive impairment or dementia (Malouf et al. 2003). The trials were unable to be pooled and there was no evidence of benefit but the trials were small and short term. For example, in the most recent trial available. 149 subjects with MCI or dementia were randomised using a 2 x 2 x 2 factorial design to receive aspirin, vitamin E and B vitamins or matching placebos Vital Trial Collaborative Group 2003. Treatment duration was for 12 weeks. No effect of treatment was found for cognitive outcomes although Hcy was lowered in the B vitamin group.
Summary and assessment of FSANZ hierarchy of evidence

65. Although there has been a massive increase in observational data suggesting an association between low folate levels and high Hcy levels and the presence of cognitive decline, dementia and AD, there is no current evidence of an effect of Hcy lowering strategies in reducing cognitive decline. For the above reasons there is only possible evidence of an association between folate and risk of cognitive decline.

Table 6. Cohort studies of association of circulating folate and homocysteine concentrations with risk of dementia and cognitive impairment

<table>
<thead>
<tr>
<th>Study Reference</th>
<th>Study Population</th>
<th>Hcy or Folate</th>
<th>Outcome</th>
<th>Age</th>
<th>Mean follow-up (yrs)</th>
<th>No of cases</th>
<th>Adjusted relative risk (95% CI)</th>
<th>Adjusted for</th>
</tr>
</thead>
<tbody>
<tr>
<td>(McCaddon et al. 2001)</td>
<td>23</td>
<td>Hcy</td>
<td>Cognitive decline</td>
<td>74</td>
<td>5 years</td>
<td>N/A</td>
<td>Hcy level predicted the rate of change in MMSE and ADAS-Cog Scores</td>
<td>Age, sex, education, renal function, vitamin B status smoking and hypertension</td>
</tr>
<tr>
<td>(Wang et al. 2001)</td>
<td>370</td>
<td>Folate</td>
<td>Incident dementia And AD</td>
<td>Over 75 years</td>
<td>3 years</td>
<td>78 dementia 60 AD</td>
<td>&lt; 10 nmol/l vs &gt; 10 nmol/l Folate level</td>
<td>Age, sex and education</td>
</tr>
<tr>
<td>(Seshadri et al. 2002)</td>
<td>1092 Subjects</td>
<td>Both</td>
<td>Incident dementia and AD</td>
<td>Mean 76 ± 6 ±</td>
<td>8 years (median)</td>
<td>111 dementia 83 AD</td>
<td>Dementia RR 1.4 (CI: 1.1, 1.9) per SD log adjusted Hcy</td>
<td>Age, sex and ApoE ε4.</td>
</tr>
<tr>
<td>(Teunissen et al. 2003)</td>
<td>144 subjects</td>
<td>Both</td>
<td>Cognitive decline</td>
<td>Mean 55</td>
<td>6 years</td>
<td>N/A</td>
<td>Hcy or folate did not correlate</td>
<td>Age, sex and education</td>
</tr>
<tr>
<td>Study Reference</td>
<td>Study Population</td>
<td>Hcy or Folate</td>
<td>Outcome</td>
<td>Age</td>
<td>Mean follow-up (yrs)</td>
<td>No of cases</td>
<td>Adjusted relative risk (95% CI)</td>
<td>Adjusted for</td>
</tr>
<tr>
<td>-----------------</td>
<td>-----------------</td>
<td>---------------</td>
<td>---------</td>
<td>-----</td>
<td>----------------------</td>
<td>-------------</td>
<td>--------------------------------</td>
<td>--------------</td>
</tr>
<tr>
<td>(Nilsson et al. 2003)</td>
<td>535 subjects</td>
<td>Hcy</td>
<td>Dementia</td>
<td>Mean 85</td>
<td>6 years</td>
<td>?</td>
<td>Not given</td>
<td>Not reported</td>
</tr>
<tr>
<td>(Luchsinger et al. 2004)</td>
<td>909 cross-sectionally</td>
<td>Hcy</td>
<td>Incident AD</td>
<td>Mean 77.2 + 6.3</td>
<td>679 people followed for 3206 person years</td>
<td>109 incident cases</td>
<td>Cross-sectional Baseline Unadjusted OR 2.0 (CI: 1.2, 3.4) Adjusted OR 1.3 (CI: 0.7, 2.3) Longitudinal Hazard Ratio (Highest quartile to lowest) 2.0 (CI 1.2, 3.5) Adjusted 1.4 (CI0.8, 2.4)</td>
<td>Age, sex, education, ApoE ε4.</td>
</tr>
<tr>
<td>(Dufouil et al. 2003)</td>
<td>1241 subjects</td>
<td>Both but only Hcy results presented</td>
<td>Cognitive decline as determined by MMSE score decrease of 3 points or more</td>
<td>Mean 67.0 + 3.0</td>
<td>2 years</td>
<td>134 (10.7%) subjects demonstrated cognitive decline</td>
<td>Compared &gt; 15 μmol/l to the group &lt; 10 μmol/l Unadjusted OR 2.8 (1.3, 6.0) Adjusted OR 2.8 (1.2, 6.2)</td>
<td>Age, sex, education, baseline cognition, BMI, alcohol, smoking, hypertension, hypercholesterolemia, glycemic status, history of vascular disease, folate and B12 levels</td>
</tr>
<tr>
<td>(Kado et al. 2005)</td>
<td>499 Subjects</td>
<td>Both</td>
<td>Cognitive decline</td>
<td>74.3 + 2.7</td>
<td>5 years</td>
<td>N/A</td>
<td>Cognitive decline determined by greatest quartile vs the rest Folate Compared the bottom quartile of folate to rest</td>
<td>Adjusted RR 1.71 (1.13, 2.37) Hcy</td>
</tr>
</tbody>
</table>
### Acknowledgements

We are grateful to Dr Peter O’Leary, Dr Liz Geelhoed and staff of the Genomics Directorate, WA Department of Health.

### References


Cho E, Spiegelman D, Hunter DJ, Chen WY, Zhang SM, Colditz GA and Willett WC. Premenopausal


McCaddon A, Hudson P, Davies G, Hughes A, Williams JH and Wilkinson C. Homocysteine and


Zhang SM, Willett WC, Selhub J, Hunter DJ, Giovannucci EL, Holmes MD, Colditz GA and Hankinson SE. Plasma folate, vitamin B6, vitamin B12, homocysteine, and risk of breast cancer.[see comment]. *Journal of the National Cancer Institute.* 2003, **95**(5): 373-80.