REVIEW

Treating vascular risk factors and maintaining vascular health: Is this the way towards successful cognitive ageing and preventing cognitive decline?

K Alagiakrishnan, P McCracken, H Feldman

Postgrad Med J 2006;**82**:101–105. doi: 10.1136/pgmj.2005.035030

Dementia is a progressive disorder that typically worsens with time and from which recovery is unlikely. The incidence of dementia increases exponentially with ageing and is an important public health challenge. There is now growing evidence for the role of vascular factors in Alzheimer's disease, mixed dementia (Alzheimer's disease with cerebrovascular disease), and of course vascular dementia. With the rising prevalence of vascular disease, there are increasing numbers of people who are identified to be at risk of cognitive impairment. By changing modifiable vascular risk factors, there is emerging evidence that it may be possible to prevent or delay the expression and progression of dementia.

The present opinion is that AD, vascular dementia (VaD), and mixed dementia (AD with cerebrovascular disease) represent a range of the same syndrome and vascular risk factors play a significant part. By changing the modifiable vascular risk factors, there is emerging evidence that it may be possible to prevent or delay the expression and progression of dementia. There is growing evidence that interventions used to control vascular factors/diseases have its effect on preventing cognitive impairment or dementia.

ANTIHYPERTENSIVE DRUGS

SHEP (systolic hypertension in the elderly program) found that treatment with a diuretic lowered the risk of stroke, but did not affect the onset of dementia. They found no differences between the groups receiving the diuretic chlorthalidone (1.6%) and placebo (1.9%).³ Guo and colleagues, showed that treatment of hypertension might protect against dementia in elderly people. In their cohort study of 1810 persons aged 75 years or older, the prevalence of dementia was significantly lower among patients being treated for hypertension than among those not taking antihypertensive drugs ($p < 0.001$). The average follow up period after baseline evaluation for hypertension and dementia was three to five years. Those receiving diuretic monotherapy had a 40% lower incidence of dementia compared with those receiving no treatment.⁴ Syst-Eur, a study on the effects of treatment in hypertensive patients over the age of 60, compared the outcomes of 1238 patients who were treated with nitrendipine with 1180 who were given placebo: 21 new cases of dementia were found in the placebo group compared with 11 cases in the treatment group. Of the incident cases of dementia, 23 were Alzheimer's dementia, two were vascular, and the other seven were felt to be mixed dementia. The investigators calculated that treating 53 people for five years would prevent one case of dementia. This study found that treatment with a calcium channel blocker (nitrendipine) lowered the rate of development of dementia to half when compared with the placebo group. Median follow up in this study was for two years.⁵ The two possible reasons that the SHEP study did not affect the onset of dementia could be (1) the mean pretreatment diastolic blood pressure was 10 mm Hg lower in the SHEP study when compared with the Syst-Eur trial and (2) the different antihypertensive used in these two studies.

Dementia is one of the most important causes of societal health problems in our greying western societies. With the predicted increase in the ageing population dementia is poised to become the largest burden of illness in the elderly. Recent scientific progress in working out the pathogenic mechanisms of dementia has been considerable, however limited to symptomatic treatments once dementia is diagnosed. There are enormous economic costs of dementia care to the health care system. It is increasingly important that where possible measures directed at preventing or delaying the onset of dementia be determined and implemented.

The Baltimore longitudinal study of ageing, reported median survival times ranging from 8.3 years for persons diagnosed as having Alzheimer's disease (AD) at age 65 years to 3.4 years for persons diagnosed at 90 years.¹ Brookmeyer *et al* reported the estimated prevalence of AD in the USA at 2.52 million, while projecting that the incidence will nearly quadruple in the next 50 years. If interventions could delay onset of AD by two years, 50 years thereafter there would be nearly two million fewer cases than currently projected. Similarly, if the onset could be delayed by only one year, there would be nearly 800 000 fewer prevalent cases.²

Little attention has been directed to the possibilities of specific strategies to delay or postpone the onset of dementia. The convergence of risk factors for AD and stroke has led some to speculate that their underlying pathogenic mechanisms begin with vascular insufficiency.

See end of article for authors' affiliations

Correspondence to:
Dr K Alagiakrishnan, c/o
Glenrose Rehabilitation
Hospital, Room 1259,
10230-111 Avenue,
Edmonton, Alberta,
Canada T5G 0B7;
kalagiak@cha.ab.ca

Submitted 14 March 2005
Accepted 27 June 2005

After the Syst-Eur trial ended in February 1997, the randomised treatment group patients were offered active study drug for a further period of observation (3.9 years overall). Treatment consisted of nitrendipine (10–40 mg/day) with the possible addition of enalapril maleate (5–20 mg/day), hydrochlorthiazide (12.5–25 mg/day) or both add on drugs. Compared with the controls, the long term antihypertensive therapy reduced the risk of dementia by 55%, from 7.4 to 3.3 cases per 1000 patient years (43 compared with 21 cases, $p < 0.001$). After adjustment for sex, age, education, and entry blood pressure, the relative hazard rate for dementia associated with the use of nitrendipine was 0.38 (95%CI, 0.23 to 0.64; $p < 0.001$). The extrapolation is that treatment of 1000 patients for five years can prevent 20 cases of dementia.⁶

The SCOPE (study on cognition and prognosis in the elderly) is a large prospective study of almost 5000 elderly patients (age 70–89 years) who are randomised to receive an angiotensin receptor antagonist candesartan, cilxetil, 8–16 mg, or placebo and this study showed a trend in the risk reduction of dementia.⁷ In the FOCUS study, the design was that of a prospective, randomised, open label, end point blinded study of 66 patients between the ages of 65 and 80 years and have untreated or poorly controlled blood pressures (systolic blood pressure 140–180 mm Hg and diastolic blood pressure 90–110 mm Hg) at entry. All patients had cognitive dysfunction and multiple white matter infarcts detected by MRI and they were randomised to receive felodipine or enalapril to doses sufficient to reduce blood pressure to $\leq 140/90$ mm Hg. Patients in both treatment groups showed statistically significant improvements in overall cognitive function at 12 weeks and 24 weeks. This is the first study to show that rigorous control of blood pressure to the currently recommended goal of $\leq 140/90$ is associated with improved cognitive function in patients with hypertension and coexisting cognitive impairment.⁸

CHOLESTEROL LOWERING DRUGS

There is, however, a growing body of biological, epidemiological, and limited randomised clinical evidence showing that lowering serum cholesterol may retard the pathogenesis of AD. It is now well known that data from observational studies suggest a possible role for statins in prevention of dementia. Two recent study reports describe an association between statin therapy and a reduction in the occurrence of AD. One report is a cross sectional analysis of discharges among three hospitals, and the other is a nested case-control study drawn from ambulatory patients of general practitioners in the UK. Wolozin B *et al* showed decreased prevalence of AD in former statin users⁹ and this finding has been supported by Jick *et al* in their nested case-control study.¹⁰ Jick and colleagues from the general practice research database identified 24 480 subjects aged 50–89 years, who had received at least one prescription for a statin at any time from the General Practice Research Database. Of them, 11 421 subjects had hyperlipidaemia, but were not treated with lipid lowering drugs. A control group of 25 000 subjects was also identified. All subjects were followed up for six years to look for the development of dementia. The relative risk in patients receiving statin treatment was reduced to 0.29 (95%CI 0.13 to 0.63; $p = 0.002$).¹⁰ Wolozin B *et al* showed a lower prevalence of diagnosed probable AD in subjects who are taking lovastatin and pravastatin.⁹ Because neither study is a randomised trial, the association noted between statin therapy and a reduced incidence of AD may have occurred because of other factors unaccounted for in the studies, may be present (so called bias) and be responsible for the observed association. Yaffe *et al* in their observational study (heart and oestrogen/progestrin

replacement study) with coronary artery disease showed women in the highest LDL cholesterol quartile had an increased likelihood of cognitive impairment (OR 1.76; 95%CI, 1.04 to 2.97). Statin users in this study had a trend for a lower likelihood of cognitive impairment (OR 0.67; 95%CI 0.42 to 1.05).¹¹

The sterol metabolism in the brain is an active process, well controlled, and regulated by 24-hydroxylase, an enzyme that is uniquely expressed in the brain.¹² ApoE has been found necessary for plaque development in animal models of AD. Animal studies have also shown that statin mediated inhibition of mevalonate synthesis is an essential reaction in forming geranylgeranyl lipid, which would lower extracellular levels of parenchymal ApoE. Suppressing ApoE secretion by statins could reduce plaques and, in turn, improve cognitive function.¹³ Fassbender *et al*, showed cholesterol lowering drug simvastatin reduce intracellular and extracellular levels of Abeta (1–42) and Abeta (1–40) peptides in primary cultures of hippocampal neurons and mixed cortical neurons in guinea pigs. Increased Abeta (1–42) levels and the epsilon 4 allele of the lipid carrier apolipoprotein E are regarded as risk factors for sporadic and familial AD.¹⁴

Rockwood *et al* did a secondary analysis of data from the Canadian study of health and ageing and found that the lipid lowering agent use was associated with a lower risk of dementia, and specifically of AD, in those younger than 80 years.¹⁵ Hajjar *et al*, in their case-control retrospective study found that the use of statins is associated with a lower prevalence of cognitive decline.¹⁶ A community based epidemiological study by Rodriguez *et al* found that demented people were associated with a lower likelihood of taking lipid lowering drugs when compared with their non-demented counterparts.¹⁷ Statins change cholesterol metabolites and reduce Abeta levels (amyloid β -peptide) deposition in the cerebrospinal fluid. A randomised, placebo controlled, double blind study from Germany evaluated 80 mg simvastatin daily compared with placebo for 26 weeks in patients with AD. The project found simvastatin significantly decreased Abeta (1–40) levels in the cerebrospinal fluid of patients with mild AD. The reduction of Abeta (1–40) correlated with the reduction of 24S-hydroxycholesterol. These changes were not seen in more severe AD patients.¹⁸

It should be noted that a large scale clinical trial with pravastatin (PROSPER) did not show the benefit of therapy. The pravastatin group achieved a 15% RRR ($p = 0.014$) in the primary end point (CVD events). Transient ischaemic attacks were decreased by 25% ($p = 0.051$). No effect on stroke or cognitive function was seen in 3.2 years. Unexpectedly low number of strokes (4.5% observed compared with 8% expected) reduced power to detect a difference in this secondary end point. However, it should be remembered that PROSPER was not powered to scrutinise for the tertiary end point of cognitive impairment.¹⁹

The enzymatic conversion of CNS cholesterol to 24S-hydroxycholesterol, which readily crosses the blood-brain barrier, is the major pathway for brain cholesterol elimination and also brain cholesterol homeostasis maintenance. Concentrations of 24S-hydroxycholesterol in plasma and cerebrospinal fluid are significantly higher in AD and vascular demented patients at early stages of the disease compared with healthy subjects. An open label study in patients with AD found statin treatment with 40 mg of lovastatin, simvastatin, or pravastatin per day for six weeks showed a reduction of 24S-hydroxycholesterol by 21.4%, LDL cholesterol by 34.9%, and total cholesterol by 25%. A group who had one gram of extended release niacin per day also showed significant reduction in 24S-hydroxycholesterol. Significant decrease in brain specific serum 24S-hydroxycholesterol

concentrations shows a diminished cholesterol metabolism in the brain.²⁰

ANTIOXIDANTS

The sequence of chemical reactions that generate energy for the body and release free radicals is called oxidation and these free radicals perpetuate constant damage. As we age the mechanisms that protect us against these molecules through the antioxidants or free radical scavengers become notably less efficient. The antioxidants are vitamins E, C, and β carotenes, metal selenium, and ginkgo biloba. With brain ageing the reactivity of the lipid oxidation product 4-hydroxy-2-nonenal (HME) with key mitochondria enzymes may be important in the age dependent loss in energy generation and increased susceptibility of neurons to apoptosis.²¹ Oxidative damage is present in the brain of AD and is seen with all biomolecules like nucleic acids, proteins, lipids, and carbohydrates. Furthermore, oxidative injury may develop secondary to excessive oxidative stress resulting from β amyloid induced free radicals, mitochondrial abnormalities, inadequate energy supply, inflammation, or changed antioxidant defences. Thus treatment with antioxidants indeed is a promising approach.²² Despite some limitations, observational studies on vitamin C, E, and carotenoids argue for a protective effect of antioxidant on cognitive performance. Rievire in their study showed vitamin C plasma levels decreased in proportion to their cognitive impairment.²³ Jimenez-Jimenez *et al* in their study compared serum levels of β carotene and vitamin A of 38 AD patients and 42 controls and they found that serum levels of β carotene and vitamin A were significantly lower in the AD group.²⁴

In a randomised, double blind, placebo controlled, multicentre trial of patients with AD of moderate severity, 341 patients were randomised to receive the selective monoamine oxidase inhibitor, selegiline (10 mg a day), α -tocopherol (vitamin E, 2000 IU/day), both selegiline and α -tocopherol, or placebo for two years. Both vitamin E and selegiline delayed the progression of the disease with vitamin E acting slightly better than selegiline. Combining the two compounds led to no further benefit. This study also showed the functional deterioration leading to nursing home placement.²⁵ In a longitudinal study by Morris *et al*, it was shown that vitamin E intake from foods or supplements, is associated with less cognitive decline with age.²⁶

However, a recent double blind placebo controlled trial with 2000 mg of vitamin E and donepezil 10 mg over a period of three years did not show any benefit in patients with mild cognitive impairment.²⁷

VITAMIN B12 AND FOLATE

Lower levels of vitamin B12 and folate in the blood are associated with cognitive symptoms. The measurement of the metabolites homocysteine and/or methylmalonic acid is recommended as a more accurate assessment of cobalamin status. According to the animal studies done in the National Institute of Aging, they have found that mice that were fed with folic acid deficient diet compared with controls had fewer brain cells in the hippocampal area that controls learning and memory. The same mice also had raised levels of homocysteine.²⁸ Renvall *et al* in their study found low levels of folate along with deficiencies of thiamine and vitamin B12 in 22 AD subjects as compared with 41 cognitively normal control group.²⁹ Serot *et al* in their study of 126 patients, including 30 patients with AD, found that the levels of folate in the cerebrospinal fluid were significantly lower in late onset AD patients.³⁰

A Swedish population based longitudinal study of 370 non-demented subjects aged 75 years and older found that subjects with low levels of B12 or folate had a twice higher

risk of developing AD over the three year period of the study.³¹ The therapeutic effects of folic acid and B vitamin supplementation were reported in a recent Austrian study, in which 9 of 31 patients with dementia and hyperhomocysteinaemia were treated with 50 mg of vitamin B1, 50 mg of vitamin B6, 5000 μ g of folic acid, and 5 μ g of vitamin B12. After four weeks of treatment, serum homocysteine concentrations returned to normal in all nine patients, decreasing from 17.3 to 10.7 μ mol/L.³²

CHOLINESTERASE INHIBITORS

SPECT studies have shown with Alzheimer's dementia progression, there is bilateral temporoparietal and hippocampal hypoperfusion.³³ Studies have also shown with different cholinesterase inhibitors the brain perfusion is preserved or it reduces the decline seen in regional blood flow in Alzheimer's dementia. Vennerica *et al* in their controlled clinical trial of rivastigmine on 27 patients with mild AD, found significant enhancement of frontal, parietal, and temporal brain blood flow with related psychometric improvement in 12 of the treated patients. A pattern of reduced cerebral flow and cognitive performance was seen in four unresponsive and 11 untreated patients.³⁴ Nakani *et al* showed in their study of 35 AD patients that donepezil treatment for one year seems to reduce the decline in regional cerebral blood flow.³⁵ These data suggest that cognitive benefits after cholinesterase therapy may be related to an increase of regional cerebral blood flow.

However, in the recent double blind, placebo controlled trials in patients with mild cognitive impairment, cholinesterase inhibitors like galantamine and donepezil were not shown to be effective in slowing down the rate of progression to AD over a period of two to three years.^{27 36}

REDUCING STRESS

Stress is an important environmental factor contributing to mental health in old age.³⁷ Glucocorticoid receptors are seen to be plentiful in the hippocampus. In fact glucocorticoids promote the loss of hippocampal neurons. The mechanism by which this happens is by potentiating ischaemic injury and oxidative stress through increased mitochondrial production of oxidants and reduction of antioxidant enzymes.³⁸ Sustained increases in cortisol are seen with depression. Studies have shown in MRI examinations of patients with late life depression enlargement of the lateral ventricles, cortical (prefrontal) and hippocampal atrophy, and the increased incidence of deep white matter and periventricular hyperintensity lesions. These findings suggest that perhaps late life depression is a manifestation of ischaemic cerebral vascular disease and vascular factors may play a part in stress and depression.^{39 40}

DIET

In the Rotterdam study of 5386 non-demented people, they showed that high intake of the following nutrients were associated with an increased risk of dementia after adjustment for confounders: total fat (RR = 2.4 (95%CI: 1.1 to 5.2)), saturated fat (RR = 1.9 (95%CI: 0.9 to 4.0)), and cholesterol (RR = 1.7 (95%CI: 0.9 to 3.2)). A high fish consumption, an important source of n-3 PUFAs (polyunsaturated fatty acids), reduced the risk of dementia (RR = 0.4 (95%CI: 0.2 to 0.9)).⁴¹ In the Zutphen elderly study, a high linoleic acid intake was found to be associated with cognitive impairment (OR = 1.8 (95%CI: 1.0 to 3.0)),⁴² whereas a high fish consumption was associated with reduced cognitive impairment or decline (RR = 0.5, 95%CI: 0.2 to 1.2). These results pointed out that a simplistic dietary intervention in addition to lipid lowering drugs could help to prevent dementia.⁴³

GLYCAEMIC CONTROL

Diabetes mellitus is a metabolic vascular risk factor of atherosclerotic disease, which results in silent infarctions or impaired cerebral blood flow because of cerebral microangiopathy and cognitive decline. Role of insulin as a neuromodulator in the brain has also been described. Two non-randomised studies of three to six months suggested that improved glycaemic control improves cognitive function in that period.⁴⁴⁻⁴⁵

EXERCISE

Regular physical activity can be a protective factor for cognitive decline and dementia. In a study by Laurin *et al* on the Canadian study of health and aging, high levels of physical activity were associated with reduced risks of cognitive impairment, especially Alzheimer's dementia (odds ratio, 0.50; 95% CI, 0.28 to 0.90) as well as dementia of other origins (odds ratio, 0.63; 95% CI, 0.4 to 0.98).⁴⁶ Another study by Colcombe *et al* showed aerobic exercise benefits on brain health in older adults and aerobic fitness reduces brain tissue loss in ageing humans.⁴⁷ Yaffe K *et al* in their study showed women with higher levels of baseline physical activity were less likely to develop cognitive decline and this association was not explained by differences in baseline function or health status.⁴⁸ The above mentioned studies showed that the simplistic lifestyle change of physical activity prevents cognitive decline.

SOCIAL LIFE

An active social life involving social network, physical leisure, and non-physical activity might protect against dementia. The Kungsholmen longitudinal study examined engagement in different activities 6.4 years before dementia diagnosis and found stimulating activity, either mentally or socially oriented related to decrease incidence of dementia. Mental, social, and productive activities produced 46%, 42%, and 42% reductions in adjusted relative risks respectively.⁴⁹

The Einstein ageing study conducted by Verghese *et al* studied the relation between leisure activities and the risk of dementia in a prospective cohort of 469 subjects older than 75 years. Their findings showed that reading, playing cards or board games such as chess, Checkers, or Scrabble, and playing a musical instrument all correlated with a lower risk of developing dementia, both Alzheimer's and vascular dementia.⁵⁰ A systematic review of 15 observational longitudinal studies on cognitive impairment and 14 on dementia provided evidence that an active and socially integrated lifestyle may be beneficial in brain ageing by reducing cognitive decline and the risk of dementia.⁵¹ Although definite mechanisms of these associations are not known, it may work through the vascular effect or by reducing stress.

ANTIPLATELET TREATMENT

Meyer *et al* in their randomised clinical trial of 70 multi-infarct dementia patients, found that the aspirin treated group showed significant improvement in cerebral perfusion values and cognitive performance scores.⁵² No other large trials have shown so far the effect of antiplatelet treatment on vascular dementia or any other dementias, even though the ongoing ASPREE trial proposes to examine possible preventive effect on vascular dementia. Inferences about the positive effects of primary prevention are based on cumulative experience with the treatment of vascular risk factors in the primary prevention of stroke, which may also help to prevent vascular dementia as well.

HORMONE REPLACEMENT THERAPY

Prospective and case-control studies showed that hormone replacement therapy might protect against AD. However,

Women Health Initiative, a randomised controlled trial, actually found that hormone replacement therapy increased the risk.⁵³ The recent MORE randomised clinical trial, showed that raloxifene, which is a selective oestrogen receptor modulator at a dose of 120 mg/day, resulted in a reduced risk of cognitive impairment in postmenopausal women. Compared with placebo women receiving 120 mg of raloxifene had a 33% lower risk of mild cognitive impairment (RR = 0.67, 95% CI 0.46 to 0.98). This effect was not seen in the group taking 60 mg of raloxifene.⁵⁴

CONCLUSION

Cognitive health is an essential component of successful ageing. Dementia seems to result from exposure to multiple factors, which can cause neurodegeneration. There is increasingly robust evidence both epidemiologically and pathologically that vascular disease contributes to cognitive impairment and dementia. There is some accruing evidence that controlling these vascular factors can prevent or postpone dementia. Adequate, practical treatment of vascular risk factors in middle age or even in old age may be the most effective preventive measure we have for the prevention of dementia at this time.

Current evidence as reviewed in this paper would suggest that to reduce cognitive decline a programme of lifestyle interventions, low fat diet, multivitamins supplementation, regular exercise, stress reduction, and adequate control of vascular risk factors particularly blood pressure and serum cholesterol are warranted pending more definite randomised controlled trials testing these combined approaches. Social integration and physical and mental stimulation for preserving healthy cognitive functioning in the elderly population is also important. The best strategies to achieve this are those that are practised over the lifespan from early adulthood or middle age. The hope is that with these interventions, we will be able to achieve healthy ageing of the brain.

Authors' affiliations

K Alagiakrishnan, P McCracken, Division of Geriatric Medicine, University of Alberta, Edmonton, Canada

H Feldman, Division of Neurology, University of British Columbia, Vancouver, Canada

Funding: none.

Conflicts of interest: none declared.

REFERENCES

- 1 Brookmeyer R, Corrada MM, Curriero FC, *et al*. Survival following a diagnosis of Alzheimer's disease. *Arch Neurol* 2002;**59**:1764-7.
- 2 Brookmeyer R, Gray S, Kawas C. Projections of Alzheimer's disease in the United States and the public health impact of delaying disease onset. *Am J Public Health* 1998;**88**:1337-42.
- 3 SHEP Cooperative Research Group. Prevention of stroke by antihypertensive drug treatment in older persons with isolated systolic hypertension. Final results of the systolic hypertension in the elderly program (SHEP). *JAMA* 1991;**265**:3255-64.
- 4 Guo Z, Fratiglioni L, Zhu L, *et al*. Occurrence and progression of dementia in community population aged 75 years and older. Relationship to antihypertensive medication use. *Arch Neurol* 1999;**56**:991-6.
- 5 Forette F, Seux ML, Staessen JA, *et al*. Prevention of dementia in randomized double-blind placebo-controlled systolic hypertension in Europe (Syst-Eur) trial. *Lancet* 1998;**352**:1347-51.
- 6 Forette F, Seux ML, Staessen JA, *et al* for the Systolic Hypertension in Europe Investigators. The prevention of dementia with antihypertensive treatment: new evidence from the systolic hypertension in Europe (Syst-Eur) study. *Arch Intern Med* 2002;**162**:2046-52.
- 7 Lithell H, Hansson L, Skoog I, *et al* for the SCOPE study group. The study on cognition and prognosis in the elderly (SCOPE); outcomes in patients not receiving add-on therapy after randomization. *J Hypertension* 2004;**22**:1605-12.
- 8 Jacobson EJ, Salehmaghaddam S, Dorman JA, *et al*. The effect of blood pressure control on cognitive function (the FOCUS study). *Am J Hypertens* 2001;**14**:55A.

- 9 **Wolozin B**, Wellman W, Rousseau P, *et al.* Decreased prevalence of Alzheimer's disease associated with 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors. *Arch Neurol* 2000;**57**:1439–43.
- 10 **Jick H**, Zornberg GL, Jick SS, *et al.* A. Statins and the risk of dementia. *Lancet* 2000;**356**:1627–31.
- 11 **Yaffe K**, Barrett-Connor E, Lin F, *et al.* Serum lipoprotein levels, statin use, and cognitive function in older women. *Arch Neurol* 2002;**59**:378–84.
- 12 **Crisby M**, Carlson LA, Winblad B. Statins in the prevention and treatment of Alzheimer disease. *Alzheimer Dis Assoc Disord* 2002;**16**:131–6.
- 13 **Naidu A**, Xu Q, Catalano R, *et al.* Secretion of apolipoprotein E by brain glia requires protein prenylation and is suppressed by statins. *Brain Res* 2002;**958**:100–11.
- 14 **Fassbender K**, Simon M, Bergmann C, *et al.* Simvastatin strongly reduces levels of Alzheimer's disease beta-amyloid peptides Abeta 42 and Abeta 40 in vitro and vivo. *Proc Natl Acad Sci U S A* 2001;**98**:5856–61.
- 15 **Rockwood K**, Kirkland S, Hogan DB, *et al.* Use of lipid-lowering agents, indication bias, and the risk of dementia in community-dwelling elderly people. *Arch Neurol* 2002;**59**:223–7.
- 16 **Hajjar L**, Schumper J, Hirth V, *et al.* The impact of the use of statins on the prevalence of dementia and the progression of cognitive impairment. *J Gerontol A Biol Sci Med Sci* 2002;**57**:M414–18.
- 17 **Rodriguez EG**, Dodge HH, Birzescu MA, *et al.* Use of lipid lowering drugs in older adults with and without dementia: a community based epidemiological study. *J Am Geriatr Soc* 2002;**50**:1852–6.
- 18 **Simons M**, Schwarzler F, Lütjohann D, *et al.* Treatment with simvastatin in normocholesterolemic patients with Alzheimer's disease: a 26-week randomized, placebo-controlled, double-blind trial. *Ann Neurol* 2002;**52**:346–50.
- 19 **Shepherd J**, Blauw GJ, Murphy MB, for the Prosper Study Group, *et al.* Pravastatin in elderly individuals at risk of vascular disease (PROSPER): randomized controlled trial. *Lancet* 2002;**360**:1623–30.
- 20 **Vega GL**, Weiner MF, Lipton AM, *et al.* Reduction in levels of 24S-hydroxycholesterol by statin treatment in patients with Alzheimer disease. *Arch Neurol* 2003;**60**:510–15.
- 21 **Floyd RA**, Hensley K. Oxidative stress in brain aging. Implications for therapeutics of neurodegenerative diseases. *Neurobiol Aging* 2002;**23**:795.
- 22 **Grundman M**, Delaney P. Antioxidant strategies for Alzheimer's disease. *Proc Nutr Soc* 2002;**61**:191–202.
- 23 **Riviere S**, Birlouvenz-Aragon I, Nourhasheni F, *et al.* Low plasma vitamin C in Alzheimer's patients despite an adequate diet. *Int J Geriatr Psychiatry* 1998;**13**:749–54.
- 24 **Jimenez- Jimenez FJ**, Molina JA, deBustos F, *et al.* Serum levels of beta carotene, alpha carotene and vitamin A in patients with Alzheimer's disease. *Eur J Neurol* 1999;**6**:495–7.
- 25 **Sano M**, Ernesto C, Thomas RG, *et al.* A controlled trial of selegiline, alpha-tocopherol, or both as treatment for Alzheimer's disease. The Alzheimer's disease co-operative study. *N Engl J Med* 1997;**336**:1216–22.
- 26 **Morris MC**, Evans DA, Bienias JL, *et al.* Vitamin E and cognitive decline in older persons. *Arch Neurol* 2002;**59**:1125–32.
- 27 **Peterson RC**, Thomas RG, Ferris S, *et al.* Vitamin E and Donepezil for the treatment of mild cognitive impairment. *N Engl J Med* 2005;**352**:2439–41.
- 28 **Kruman II**, Kumaravel TS, Lohani A, *et al.* Folic acid deficiency and homocysteine impair DNA repair in hippocampal neurons and sensitize them to amyloid toxicity in experimental models in Alzheimer's disease. *J Neurosci* 2002;**22**:1752–62.
- 29 **Rennvall MJ**, Spindler AA, Ramsdell JW, *et al.* Nutritional status of free-living Alzheimer's patients. *Am J Med Sci* 1989;**298**:20–7.
- 30 **Serot JM**, Christmann D, Dubost T, *et al.* CSF folate levels are decreased in late-onset AD patients. *J Neural Transm* 2001;**108**:93–9.
- 31 **Wang HX**, Wahlén A, Basun H, *et al.* Vitamin B12 and folate in relation to the development of Alzheimer's disease. *Neurology* 2001;**56**:1188–94.
- 32 **Leblhuber F**, Walli J, Arner- Dworzak E, *et al.* Homocysteine and B vitamins in dementia. *J Neural Transm* 2000;**107**:1469–74.
- 33 **Rodriguez G**, Vitali P, Calvini P, *et al.* Hippocampal perfusion in mild Alzheimer's disease. *Psychiatry Res* 2000;**100**:65–74.
- 34 **Vennerica A**, Shanks HG, Murray AD. Cerebral blood flow and cognitive responses to rivastigmine treatment in Alzheimer's disease. *Neuroreport* 2002;**13**:83–7.
- 35 **Nakano S**, Asada T, Matsuda H, *et al.* Donepezil hydrochloride preserves regional cerebral blood flow in patients with Alzheimer's disease. *J Nucl Med* 2001;**42**:1441–5.
- 36 **Mayor S**. Regulatory authorities review use of galantamine in mild cognitive impairment. *BMJ* 2005;**33**:276.
- 37 **Seeman TE**, Singer BH, Rowe JW, *et al.* Price of adaption-allostatic load and its health consequences. MacArthur studies of successful aging. *Arch Intern Med* 1997;**157**:2259–68.
- 38 **Liv J**, Mori A. Stress, aging and brain oxidative damage. *Neurochem Res* 1999;**24**:11479–97.
- 39 **Krishnan KR**, Gadde KM. The pathophysiologic basis for late life depression. Imaging studies of the aging brain. *Am J Geriatr Psychol* 1996;**4**(suppl 1):S22–33.
- 40 **Sheline YI**, San Ghavi M, Mintum MA, *et al.* Depression duration but not age predicts hippocampal volume loss in medically healthy women with recurrent major depression. *J Neurosci* 1999;**19**:5034–43.
- 41 **Kalmijn S**, Launer UJ, Ott A, *et al.* Dietary fat intake and the risk of incident dementia in the Rotterdam study. *Ann Neurol* 1997;**42**:776–82.
- 42 **Kalmijn S**, Feskens EJ, Launer UJ, *et al.* Polyunsaturated fatty acids, anti oxidants and cognitive function in very old men. *Am J Epidemiol* 1997;**145**:33–41.
- 43 **Kalmijn S**. Fatty acid intake and the risk of dementia and cognitive decline: a review of clinical and epidemiological studies. *J Nutr Health Aging* 2000;**4**:202–7.
- 44 **Gradman TJ**, Laws A, Thompson LW, *et al.* Verbal learning and/or memory improves with glycemic control in older subjects with non-insulin dependent diabetes mellitus. *J Am Geriatr Soc* 1993;**41**:1305–12.
- 45 **Meneilly GS**, Cheung E, Tessier D, *et al.* The effect of improved glycemic control on cognitive functions in the elderly patients with diabetes. *J Gerontol A Biol Med Sci* 1993;**48**:M117–21.
- 46 **Laurin D**, Verreault R, Lindsay J, *et al.* Physical activity and risk of cognitive impairment and dementia in elderly persons. *Arch Neurol* 2001;**38**:498–504.
- 47 **Colcombe SJ**, Erickson KI, Raz N, *et al.* Aerobic fitness reduces brain loss in aging humans. *J Gerontol A Biol Sci Med Sci* 2003;**58**:M176–80.
- 48 **Yaffe K**, Barnes D, Nevitt M, *et al.* A prospective study of physical activity and cognitive decline in elderly women: women who walk. *Arch Intern Med* 2001;**161**:1703–8.
- 49 **Wang HX**, Karp A, Winblad B, *et al.* Late-life engagement in social and leisure activities is associated with a decreased risk of dementia: a longitudinal study from the Kungsholmen project. *Am J Epidemiol* 2002;**155**:1081–7.
- 50 **Verghese J**, Lipton RB, Katz MJ, *et al.* Leisure activities and the risk of dementia in the elderly. *N Engl J Med* 2003;**348**:2508–16.
- 51 **Fratiglioni L**, Paillard- Borg S, Winblad B. An active and socially integrated lifestyle in late life might protect against dementia. *Lancet Neurol* 2004;**3**:343–53.
- 52 **Meyer JS**, Rogers RL, Mc Clintic K, *et al.* Randomized clinical trial of daily aspirin therapy in multi-infarct dementia. A pilot study. *J Am Geriatr Soc* 1989;**37**:549–55.
- 53 **Shumaker SA**, Legault TC, Rapp SR, *et al.* Estrogen plus progestin and the incidence of dementia and mild cognitive impairment in post menopausal women. *JAMA* 2003;**289**:2651–62.
- 54 **Yaffe K**, Krueger K, Cummings SR, *et al.* Effect of raloxifene on prevention of dementia and cognitive impairment in older women: The multiple outcomes of raloxifene evaluation (MORE) randomized trial. *Am J Psychiatry* 2005;**162**:683–90.