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PEER REVIEWED FEATURE
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Brain and heart targets for better dementia prevention

Key points

- Dementia forecasts suggest a quadrupling of affected individuals in Australia to over one million by 2050.
- Given this prediction, it will not be medically or econo - mically feasible to carry on with the current practice of dementia care.
- Better dementia prevention must therefore be a national priority and requires a whole-of-society approach.
- Absolute dementia preven - tion is not possible, but better prevention should be achievable at the population level.
- Cultivating an active cognitive lifestyle, particularly after retirement, is one key anti-dementia strategy.
- Reduction of cardiovascular risk factors, especially hypertension, in people aged in their forties and fifties is another important strategy.

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Although absolute prevention of dementia is not possible, better dementia prevention is certainly achievable and of utmost importance. A new emphasis on promoting an active cognitive lifestyle along with cardiovascular risk factor reduction is recommended.

Ageing populations worldwide mean that, with the current trends, the burden of dementia-related disease risks sinking modern healthcare practice. Dementia currently affects 260,000 Australians and 34 million individuals worldwide. Continuation of the status quo will see an almost quadrupling by 2050, devastating the lives of one million Australians, along with the associated effects on their families and friends.[1] Dementia being a terminal illness, it is likely that dementia and other age-related neurodegenerative disorders will become the leading cause of death within this timeframe. At the same time, spending on dementia will rise to $83 billion, approximating the entire current health budget, and accounting for 11% of predicted health-related spending.[2]

Driving these changes is the ageing of modern society and also the nexus between advanced age and dementia risk: dementia prevalence is 0.9% in people aged 60 to 64 years, rising to 12.2% in those aged 80 to 84 years, and to more than 35.7% in those over 90 years of age.[3] The sustainability of current healthcare practice and funding will therefore come under severe strain, as already witnessed in other countries.[4]

In order to avert these dire predictions, a healthy brain ageing agenda needs to rise to prominence at all levels of medical practice, among health policy makers and in the wider community. There are several preventive actions that GPs can encourage to help mitigate dementia risk. Given that many of the aetiological factors implicated in dementia

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begin 20 to 30 years before symptom onset, for maximum effectiveness GPs need to target not only those people already in the at-risk older age range but also those in their forties and fifties.[5,6]

COGNITIVE LIFESTYLE AND BRAIN HEALTH

Cognitive lifestyle refers to a person's history and ongoing engagement with complex mental activities.[7,8] In practical terms, it is defined in relation to educational activities and occupational challenge and complexity as well as cognitive-loaded leisure activities. In a systematic review of 22 long-term cohort studies, it has been found that each of these three major components of cognitive lifestyle was associated with reduced risk of incident dementia by between 40 and 50%.[9] Overall, a more active cognitive lifestyle was linked to a 46% reduction in incident dementia compared with an impoverished cognitive lifestyle.

The link between cognitive lifestyle and dementia risk has since been replicated in numerous studies, including the large Cognitive Function and Ageing Study (CFAS) based in the United Kingdom, in which more than 13,000 individuals were followed up for more than 13 years.[7] This study showed that no single component of cognitive lifestyle was by itself strongly associated with reduced dementia risk; rather, it was a combination of increased mental activity from the educational, occupational and lifestyle areas that was important – in this study, predictive of a 40% reduction in dementia incidence. Cognitive lifestyle and dementia risk therefore appear to be intimately related.

The possibility that these findings may be explained by 'reverse causality', where a drop-off in participation in complex activities occurs during the long prodrome before clinical diagnosis of dementia, is difficult to rule out on the basis of observational studies alone. However, the mechanistic and clinical trials research reviewed below indicates that stimulating an individual's cognitive lifestyle in late life can indeed have a positive impact on long-term cognition.

ASSESSING AND IMPROVING COGNITIVE LIFESTYLE

Assessment

The Lifetime of Experiences Questionnaire (LEQ) was specifically designed to assess a cognitively-intact older person's cognitive lifestyle.[10] Scores are derived from both retrospective and contemporaneous accounts of educational, occupational and cognitively-demanding lifestyle activities across three phases of life – young adulthood, midlife and late life. Higher LEQ scores indicate a more active cognitive lifestyle and predict both a slower rate of future cognitive decline, as well as a reduced rate of hippocampal atrophy.[11]

To facilitate use in the community, the LEQ can be completed online at www.rng.org.au/leq Completion takes about 15 minutes and gives users feedback in the form of a percentile score, along with information about how to interpret the score. Note that interpretation of LEQ in those with diagnosed dementia, questionable dementia, mild cognitive impairment or borderline cognition is not possible.

Response to assessment

Individuals with a LEQ percentile score of less than 60% are at risk for cognitive decline, and should be specifically encouraged to participate in a new, complex mental activity that requires ongoing learning and social engagement. Although the long-term benefits to brain health of commencing such activities are yet to be fully understood, the risks are minimal and potential positive effects may generalise beyond the cognitive to include enhanced mood, self-empowerment and quality of life.

Recommendations for increasing mental activity include:

- learning a new language
- enrolling in a course or formal education
- running a course or teaching others
- learning to play a musical instrument, draw, paint or another artistic pursuit
- learning a new complex skill such as carpentry, embroidery or dancing
- joining a book club
- joining a volunteer organisation
- helping teachers at a local school.

The assessment of a cognitively-intact older person's cognitive lifestyle is discussed further in the box on this page.[10,11]

MECHANISMS UNDERLYING COGNITIVE LIFESTYLE

How might an active cognitive lifestyle lead to reduced rates of dementia? Animal studies suggest many different neuroplastic mechanisms are likely to be involved in this process.[12,13] For example, an enriched environment for a rodent (including more toys, running wheels and littermates in the animal's home cage) induces a host of neuroplastic changes in

adult animals, even in old age.[14] These changes range from dozens of alterations in gene expression pathways to increased production of neurotrophic hormones, greater synaptic plasticity, upregulated neurogenesis and, controversially, Alzheimer's disease modification in transgenic models.

The relevance to humans of these findings is only beginning to be understood. In the largest study of its kind, the Epidemiological Clinicopathological Studies in Europe (EClipSE) transnational neuropathology collaboration examined the relation between Alzheimer's disease pathology, cognitive state and level of education attained in young adulthood.[15] Education was not linked to any measure of neuropathology and so discounts a possible mechanism, Alzheimer's disease modification. Education did, however, have a dramatic modulatory effect on the link between pathology and cognition. All of the elderly individuals with four to seven years of education and moderate to severe neuritic plaques in the hippocampus were clinically demented at their ultimate cognitive assessment. In contrast, 43% of those with 12 or more years of education and the same level of hippocampal neuropathology remained dementia-free. A higher level of education in youth may therefore allow individuals to compensate for the build-up of pathology in the brain in later life, to the extent that many will not show clinical symptoms of the pathology.

The frontal lobe is likely to be an important region for mediating these compensatory effects. Our research has found that individuals with a more active cognitive lifestyle have a greater density of neurons in the prefrontal cortex, accompanied by a thicker neocortex in the same region.[16] These results are consistent with neuroimaging studies that show increased frontal lobe cortical activation in individuals who 'age successfully' by virtue of proficient cognitive abilities.[17,18] Together these results suggest that cortical compensation is an important and possibly uniquely human mechanism.

Interestingly, evidence has also been found for an otherwise overlooked mechanism, modification of cerebrovascular disease.[16] Men with a more active cognitive lifestyle were at 70 to 80% lower risk for lacunes, atherosclerosis and deep white matter lesions in the brain than those with a low cognitive lifestyle, even after accounting for differences in vascular risk factors. Because cerebrovascular disease can itself lead to cognitive impairment and dementia, as well as potentiate the clinical effect of Alzheimer's disease pathology, an active cognitive lifestyle may lead to lower dementia risk by modifying this disease process.[19-21]

CLINICAL TRIALS OF BRAIN TRAINING

Cognitive or brain training refers to repeated exercise on standardised tasks with an embedded problem or challenge that targets specified cognitive domains.[20] There are many brain training packages available commercially, in either booklet, computer software or internet format, and of vastly variable quality and evidence base. For guidelines and tips about choosing a respectable brain training package, refer to the Consumer Information Statement available under the 'Does your brain need training' newsflash item at www.brainage.med.unsw.edu.au.

Cognitive training can be thought of as one of the more focused, specific and, arguably, potent forms of cognitive life - style activities. A systematic review of randomised controlled trials of cognitive training with long-term follow up in healthy elderly individuals found evidence for a strong and positive effect size on cognitive and functional outcomes, but the field has been limited by small sample sizes and design issues.[23] In mild cognitive impairment, there is mixed evidence for possible efficacy of this training, but again the area is notable for the lack of large, high-quality studies.[24] In established dementia, however, there is little evidence for the efficacy of brain training in changing cognitive trajectory.[25] Cognitive training may, therefore, have a useful role in the primary and secondary prevention of dementia, but further research is required.

RETHINKING RETIREMENT

Brain training is not the only way to boost a person's cognitive lifestyle. There are a host of lifestyle activities with inherent cognitive demands that may also be effective (see the box on page 39).

One of these activities is volunteerism, as illustrated by the Experience Corps study. This study of older cognitively-intact African American women at increased risk for dementia because of one or more cardiovascular disease risk factors found that volunteer activity at a local primary school produced several positive cerebral blood flow effects in the frontal lobe, reversing some of the changes often seen with advanced age.[26]

Another activity is becoming proficient in a second language, which has been associated with a 4.3-year delay in dementia diagnosis and symptoms.[27] Although these kinds of cognitive lifestyle interventions may have a powerful impact on the brain, they are yet to be investigated in the context of clinical trials with dementia prevention outcomes. However, given the very low risk for adverse effects and the possible long-term benefits to mental health, it is reasonable for clinicians to recommend engaging in these kinds of activities, particularly after retirement.

The broader issue of what society expects from retirement may also need revision. A recent econometric study found a clear correlation between a nation's mandated age of retirement and that population's average level of memory proficiency in later life.[28] Stopping

work at a relatively younger age and 'switching off mentally' is detrimental to long-term cognitive function. Extending the retirement age indefinitely is, however, not a palatable personal or policy option. Rather, a whole-of-society approach to enriching the cognitive lifestyle of retirees is required. Suggestions for challenging the mind include undertaking formal education, learning new skills, teaching others and volunteerism.

HEART HEALTH AND DEMENTIA PREVENTION

Virtually every known cardiovascular (CV) risk factor also confers a heightened risk for dementia, including both Alzheimer's disease and vascular dementia.[29,30] Although each CV risk factor is likely to have its own specific way of contributing to neuronal loss and dysfunction, and hence dementia, the reason for a common risk is clear: neurons need a decent blood supply for proper brain function. In the same way that CV risk factors can lead to arteriosclerosis in the heart's blood vessels, and ultimately myocardial infarction, similar pathology can affect both the large and small vessels of the brain (macro- and microcerebrovascular disease, respectively), and culminate in cerebral infarction.

Following conventional definitions, 25 to 30% of individuals will develop vascular dementia in the 12 months following a stroke.[31] There is therefore an entirely logical and reasonable expectation that better prevention of stroke (both declared and silent) should help prevent vascular dementia. Moreover, there is ample evidence for the primary prevention of stroke based on the simple elimination of CV risk factors. For example, clinical trials show that better management of hypertension in the elderly reduces the risk for stroke by between 30 and 42%.[32,33] On first principles, aggressive targeting of hypertension and other CV risk factors should help reduce the incidence of vascular dementia.

DEMENTIA PREVENTION: THREE TAKE-HOME MESSAGES FOR PATIENTS

Population-based health prevention campaigns are notoriously ineffective when dissociated from a feared outcome. GPs and other health professionals have therefore often ignored one of their most effective weapons for driving behavioural change: the almost preternatural fear within the community of developing a neurodegenerative brain disorder. In community surveys, Alzheimer's disease and dementia are consistently ranked as one of the most feared health conditions.

For this reason, GPs should take the opportunity in consultations with patients to acknowledge that dementia risk increases significantly with age after 65 years and to explain that there are several steps that can be taken to minimise or mitigate this risk. These steps are presented below as three 'take-home messages' for patients.

1. Healthy heart, healthy mind: don't ignore hypertension

In the community, hypertension is the least well-understood risk factor for dementia.[44] Educate patients that their having high blood pressure when they are aged in their forties and fifties increases their risk of having dementia in their sixties and seventies by two to three times. Treating hypertension at any age reduces the long-term risk of dementia.

2. Use it or lose it: take on new activities with a mental and social challenge

Australians often correctly cite 'mental activity' as a modifiable dementia risk factor. Emphasise this to patients by explaining that, like a muscle, the brain requires regular challenging activity in order to remain healthy and strong. Explain that the level of mental challenge needs to be high – crosswords or sudoku is not enough. Greater social engagement is also a strong predictor of decreased dementia risk.

3. Physical exercise promotes mental fitness

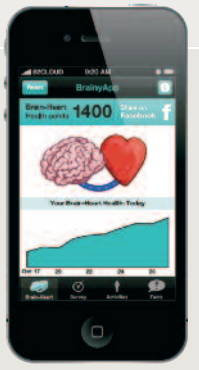
Although the benefits of regular physical exercise on general health are obvious, exercise also leads to positive physical changes in the brain. Tell patients this, and explain that regular physical exercise slows the rate of cognitive decline in those individuals most at risk for dementia, and so is one of the most important preventive health activities.

The relation between CV risk factors and Alzheimer dementia is more complex but is potentially equally rewarding from a primary prevention perspective.[34] There is a growing awareness that the classic distinction between Alzheimer and vascular dementia is problematic as the pathologies occur simultaneously in the brains of older individuals more often than each occurs alone.[35,36] In the community, 'mixed dementia' is therefore the most likely default aetiology, an interaction of both Alzheimer pathology and cerebrovascular disease.[37,38]

By better identifying and treating CV risk factors, GPs may be better able to prevent sporadic dementia in general. Hypertension, physical exercise and smoking are the CV risk factors suggested as being particularly promising heart health targets. GPs should discuss dementia prevention with patients in their forties and fifties, well before the age of usual symptom onset (see the box on this page).

'BRAINYAPP'

'BrainyApp' is an iPhone/iPad application designed to increase the user's awareness of dementia risk factors as well as act a personalised tool to help drive positive behavioural change. An initiative of Alzheimer's Australia in partnership with the Bupa Health Foundation and in collaboration with Dr Michael Valenzuela, it is available free of charge at the Apple App Store. For more information go to www.brainyapp.com.au.



An iPhone/iPad application has been developed to increase awareness of dementia risk factors as well as to help drive positive behavioural change (see the box on this page).

Diagnose and manage hypertension

Several large long-term epidemiological studies have noted that midlife hypertension is associated with a two- to threefold increase in dementia risk some 20 to 30 years later (including both Alzheimer and vascular dementia); furthermore, this association appears to be independent of other CV risk factors.[39,40] Epidemiological links between hypertension in late life and dementia incidence are less consistent, and almost certainly confounded by the well-described reduction in blood pressure in the years leading up to dementia diagnosis (often dropping to hypotensive levels).[41]

On the other hand, treatment of simple hypertension in the elderly (over 60 years of age) is the only medical intervention found so far to reduce the incidence of dementia (both Alzheimer and vascular) in a double-blind, placebo-controlled, randomised clinical trial (the Systolic Hypertension in Europe [Syst-Eur] trial).[32] Interestingly, this protective and preventive effect against dementia became stronger after several years of open-label follow up.[42]

The Syst-Eur trial was unique for employing a calcium channel blocker as first-line therapy, an approach and outcome not since replicated. Other randomised controlled trials of antihypertensives have used other classes of antihypertensive drugs as first-line treatment, with mixed results. A recent meta-analysis of these trials suggests a modest effect of reduced dementia incidence with antihypertensive treatment,[43] and highlights how these trials were primarily designed to assess cardiac and stroke outcomes, not dementia, and so employed very limited cognitive techniques. Further large-scale randomised controlled trials with dementia prevention as the primary outcome measure are urgently required.

There is a reasonable evidence base suggesting that enhanced blood pressure management in both midlife and late life can reduce dementia incidence.[34] The link between hypertension and dementia is not commonly known in the community,[44] and so represents an excellent opportunity for GPs to educate their patients, as well as help motivate better compliance for a condition that has notoriously low treatment adherence rates (see the box on page 41).

Physical exercise

There is overwhelming basic science, epidemiological and clinical trials evidence that physical exercise is beneficial to brain health, particularly for older individuals.[45-48] The mechanisms underlying this are complex, and include systemic adaptations related to cytokine response to inflammation, metabolic up-regulation and increased cardiac output, as well as central changes related to improved cerebral blood flow and a whole spectrum of neuroplastic mechanisms.[49]

A recent large Australian clinical trial in individuals with mild cognitive impairment found that regular, self-managed and moderate intensity aerobic exercise (mainly walking) significantly reduced the rate of cognitive decline, albeit with modest effect size.[47] The precise dosage and pattern of physical exercise required for cognitive benefits is currently unclear. A reasonable working assumption is that the regimen found time and again to be effective for systemic illnesses such as coronary artery disease, arthritis, osteoporosis and pre-diabetes may also be effective for preventing cognitive dysfunction.[50] This regimen is therefore considered the default recommendation, and consists of aerobic exercise:

- of moderate intensity ('sufficient intensity that you could talk at the same time, but not sing')
- at least three times a week
- lasting 30 to 45 minutes per session.

The issue of whether progressive resistance or strength training is as effective as aerobic exercise for cognitive outcomes is wholly untested. Strength training stimulates many of the same anti-inflammatory and prometabolic pathways as aerobic exercise, and appears to be particularly effective for preventing diabetes.[51] This may be especially relevant to dementia prevention because of emerging direct links between dementia risk and each of midlife diabetes and obesity.[52,53] Further research is required to determine whether strength training alone or in combination with aerobic exercise is useful for preventing cognitive dysfunction in later life.

Smoking cessation

Despite some persistent urban myths to the contrary, epidemiological studies

consistently link smoking and increased dementia risk.[54] Furthermore, long-term cohort studies indicate that the risk for dementia in former smokers approaches, after several years from quitting, that of never smokers, and so smoking may be an important modifiable risk factor.[54]

Clinical trials of dementia prevention based on cessation of smoking are currently under design. Meanwhile, GPs can educate patients that apart from the well-known links between smoking and cardiac disease and cancer, smoking also increases the risk for dementia. In the long term, stopping smoking is likely to also reduce dementia risk.

Dietary advice – omega-3 fatty acids

No diet, nutrient or vitamin supplement has been shown in a randomised controlled trial to prevent the development of dementia. On the other hand, there is strong evidence that both omega-3 fatty acid supplementation and oily fish consumption (two or three times a week) reduce the rate of major cardiovascular events such as myocardial infarction.[55]

Given the close links referred to above between vascular integrity and dementia, it is probable that long-term adherence to a Mediterranean diet (i.e. mainly fish, fresh fruit and vegetables) will lower an individual's risk for stroke, and may possibly help lower his or her risk for dementia.[56] Oily fish include salmon, tuna, swordfish, mackerel and sardines. Awareness of the relative contraindications of eating seafood (such as not eating raw seafood or seafood with high levels of mercury during pregnancy) and ecological considerations (such as the sustainability of the seafood; see www.sustainableseafood.org.au) are also recommended.

EXPECTATION MANAGEMENT: SMALL GAINS, BIG IMPACT

Dementia cannot be definitively prevented, and prevention in this area is a relative term. The evidence to date suggests that a multifactorial strategy targeting both cognitive lifestyle promotion and cardiac risk factor elimination (particularly hypertension) is likely to lower the risk of incident dementia compared with the status quo.

Accordingly, there are no guarantees that an individual will not develop dementia, but simply a series of recommendations on how to best lower a person's odds of getting the disease. In reality this may mean an individual develops dementia at a later age than otherwise, or during this extended dementia-free period dies naturally from another cause. Although this may appear a modest gain, the population and societal impacts could be enormous: for example, a five-year delay in dementia presentation would translate to a 43% reduction in dementia prevalence.[57]

CONCLUSION

Dementia is becoming one of medicine's most pressing issues, and there is a lot more that can be done in the primary care setting to help avert the forecast epidemic. Increased attention to cultivating an active cognitive lifestyle, particularly after retirement, accompanied by a greater focus on the elimination of cardiovascular risk factors in the 10 to 20 years leading up to retirement are two simple and potentially powerful strategies to help prevent dementia.

GPs should take advantage of the deep-seated fear of dementia in the community to foster positive behavioural change in their patients that may ultimately benefit both brain and body health. MT

REFERENCES

A list of references is available on request to the editorial office.

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REFERENCES

1. Brookmeyer R, Johnson E, Ziegler-Graham K, Arrighi H. Forecasting the global burden of Alzheimer's disease. Alzheimers Dement 2007; 3: 186-191.
2. Access Economics, for Alzheimer's Australia. Keeping dementia front of mind: incidence and prevalence 2009–2050. Access Economics Pty Ltd; 2009. p. 86.
3. Access Economics, for Alzheimer's Australia. Dementia estimates and projections: Australian states and territories. Access Economics Pty Ltd; 2005. p. 4.
4. Economist. A slow-burning fuse: a special report on ageing populations. London: The Economist Newspaper Ltd, 25 June 2009.
5. Jack CR Jr, Knopman DS, Jagust WJ, et al. Hypothetical model of dynamic biomarkers of the Alzheimer's pathological cascade. Lancet Neurol 2010; 9: 119-128.
6. Savica R, Petersen RC. Prevention of dementia. Psychiatr Clin North Am 2011; 34: 127-145.
7. Valenzuela M, Brayne C, Sachdev P, Wilcock G, Matthews F; Medical Research Council Cognitive Function and Ageing Study. Cognitive lifestyle and long-term risk of dementia and survival after diagnosis in a multicentre population-based cohort. Am Epidemiol 2011; 173: 1004-1012.
8. Valenzuela M. Cultivating a cognitive lifestyle: implications for healthy brain ageing and dementia prevention. In: McNamara P (ed). Dementia. Volume 1: History and incidence. Santa Barbara, CA: Praeger; 2011. p. 99-122.
9. Valenzuela MJ, Sachdev P. Brain reserve and dementia: a systematic review. Psychol Med 2006; 36: 441-454.
10. Valenzuela MJ, Sachdev P. Assessment of complex mental activity across the lifespan: development of the Lifetime of Experiences Questionnaire (LEQ). Psychol Med 2007; 37: 1015-1025.
11. Valenzuela M, Sachdev P, Wen W, Chen X, Brodaty H. Lifespan mental activity predicts diminished rate of hippocampal atrophy. PLoS One 2008; 3: e2598.
12. Valenzuela MJ, Breakspear M, Sachdev P. Complex mental activity and the aging brain: molecular, cellular and cortical network mechanisms. Brain Res Rev 2007; 56: 198-213.
13. Nithianantharajah J, Hannan AJ. Enriched environments, experience-dependent plasticity and disorders of the nervous system. Nat Rev Neurosci 2006; 7: 697-709.
14. Kempermann G, Fabel K, Ehninger D, et al. Why and how physical activity promotes experience-induced brain plasticity. Front Neurosci 2010; 4: 189.
15. Brayne C, Ince P, Keage H, et al; EClipSE Collaborative Members. Education, the brain and dementia: neuroprotection or compensation? Brain 2010; 133: 2210-2216.
16. Valenzuela M, Matthews F, Brayne C, et al. Medical Research Council Cognitive Function and Ageing Study. Multiple biological pathways link cognitive lifestyle to protection from dementia. Biol Psychiatry. Epub ahead of print 2 Nov 2011.
17. Cabeza R, Anderson N, Locantore J, McIntosh A. Aging gracefully: compensatory brain activity in high-performing older adults. Neuroimage 2002; 17: 1394-1402.
18. Grady CL, McIntosh AR, Beig S, Keightley ML, Burian H, Black SE. Evidence from functional neuroimaging of a compensatory prefrontal network in Alzheimer's disease. J Neurosci 2003; 23: 986-993.
19. Dufouil C, Godin O, Chalmers J, et al. Severe cerebral white matter hyperintensities predict severe cognitive decline in patients with cerebrovascular disease history. Stroke 2009; 40: 2219-2221.
20. van Straaten EC, Harvey D, Scheltens P, et al. Periventricular white matter hyperintensities increase the likelihood of progression from amnestic mild cognitive impairment to dementia. J Neurol 2008; 255: 1302-1308.
21. Snowdon DA, Greiner LH, Mortimer JA, Riley KP, Greiner PA, Markesbery WR. Brain infarction and the clinical expression of Alzheimer disease. The Nun Study. JAMA 1997; 277: 813-817.
22. Gates N, Valenzuela M. Cognitive exercises and its role in cognitive function in the elderly. Curr Psychiatry Rep 2010; 12: 20-27.
23. Valenzuela M, Sachdev P. Can cognitive exercise prevent the onset of dementia? systematic review of randomized clinical trials with longitudinal follow-up. Am J Geriatr Psychiatry 2009; 17: 179-187.
24. Gates N, Sachdev P, Fiatarone Singh M, Valenzuela M. Cognitive and memory training in adults at risk of dementia: a systematic review. BMC Geriatr 2011; 11: 55.
25. Sitzer DI, Twamley EW, Jeste DV. Cognitive training in Alzheimer's disease: a meta-analysis of the literature. Acta Psychiatr Scand 2006; 114: 75-90.
26. Carlson MC, Erickson KI, Kramer AF, et al. Evidence for neurocognitive plasticity in at-risk older adults: the experience corps program. J Gerontol A Biol Sci Med Sci 2009; 64: 1275-1282.
27. Craik FI, Bialystok E, Freedman M. Delaying the onset of Alzheimer disease: bilingualism as a form of cognitive reserve. Neurology 2010; 75: 1726-1729.
28. Rohwedder S, Willis RJ. Mental retirement. J Econ Perspect 2010; 24: 119-138.
29. Kivipelto M, Ngandu T, Laatikainen T, Winblad B, Soininen H, Tuomilehto J.

Risk score for the prediction of dementia risk in 20 years among middle aged people: a longitudinal, population-based study. Lancet Neurol 2006; 5: 735-741.
30. Luchsinger J, Reitz C, Honig L, Tang M, Shea S, Mayeax R. Aggregation of vascular risk factors and risk of incident Alzheimer's disease. Neurology 2005; 65: 545-551.
31. Sachdev P, Brodaty H, Valenzuela M, et al. The neuropsychological profile of vascular cognitive impairment in stroke and TIA patients. Neurology 2004; 62: 912-919.
32. Forette F, Seux ML, Staessen JA, et al. Prevention of dementia in randomised double-blind placebo-controlled Systolic Hypertension in Europe (Syst-Eur) trial. Lancet 1998; 352: 1347-1351.
33. Beckett NS, Peters R, Fletcher AE, et al. Treatment of hypertension in patients 80 years of age or older. N Engl J Med 2008; 358: 1887-1898.
34. Gorelick PB, Scuteri A, Black SE, et al. Vascular contributions to cognitive impairment and dementia: a statement for healthcare professionals from the American Heart Association/American Stroke Association. Stroke 2011; 42: 2672-2713.
35. Schneider JA, Arvanitakis Z, Bang W, Bennett DA. Mixed brain pathologies account for most dementia cases in community-dwelling older persons. Neurology 2007; 69: 2197-2204.
36. Neuropathology Group of the Medical Research Council Cognitive Function and Ageing Study (MRC CFAS). Pathological correlates of late-onset dementia in a multicentre, community-based population in England and Wales. Lancet 2001; 357: 169-175.
37. Korczyn AD. Mixed dementia – the most common cause of dementia. Ann N Y Acad Sci 2002; 977: 129-134.
38. Langa KM, Foster NL, Larson EB. Mixed dementia: emerging concepts and therapeutic implications. JAMA 2004; 292: 2901-2908.
39. Launer LJ, Masaki K, Petrovich H, Foley D, Havlik R. The association between midlife blood pressure levels and late-life cognitive function. JAMA 1995; 274: 1846-1851.
40. Kivipelto M, Helkala E, Laakso M, et al. Apolipoprotein E e4 allele, elevated midlife cholesterol and high midlife systolic blood pressure are independent risk factors for late-life Alzheimer's disease. Ann Intern Med 2002; 137: 149-155.
41. Skoog I, Lernfelt B, Landahl S, et al. 15-year longitudinal study of blood pressure and dementia. Lancet 1996; 347: 1141-1145.
42. Forette F, Seux ML, Staessen JA, et al. The prevention of dementia with antihypertensive treatment: new evidence from the Systolic Hypertension in Europe (Syst-Eur) study. Arch Intern Med 2002; 162: 2046-2052.
43. Peters R, Beckett N, Forette F, et al. Incident dementia and blood pressure lowering in the Hypertension in the Very Elderly Trial cognitive function assessment (HYVET-COG): a double-blind, placebo controlled trial. Lancet Neurol 2008; 7: 683-689.
44. Farrow M. Dementia risk reduction: what do Australians know? Alzheimer's Australia Paper 14. Canberra: Alzheimer's Australia; 2008.
45. Cotman CW, Berchtold NC. Physical activity and the maintenance of cognition: learning from animal models. Alzheimers Dement 2007; 3(2 Suppl): S30-37.
46. Hillman C, Erickson K, Kramer A. Be smart, exercise your heart: exercise effects on brain and cognition. Nat Rev Neurosci 2008; 9: 58-65.
47. Lautenschlager NT, Cox KL, Flicker L, et al. Effect of physical activity on cognitive function in older adults at risk for Alzheimer disease: a randomized trial. JAMA 2008; 300: 1027-1037.
48. Baker LD, Frank LL, Foster-Schubert K, et al. Effects of aerobic exercise on mild cognitive impairment: a controlled trial. Arch Neurol 2010; 67: 71-79.
49. Valenzuela M. Maintain your brain. Sydney: ABC Books; 2011.
50. Gleeson M, Bishop NC, Stensel DJ, Lindley MR, Mastana SS, Nimmo MA. The anti-inflammatory effects of exercise: mechanisms and implications for the prevention and treatment of disease. Nat Rev Immunol 2011; 11: 607-615.
51. Umpierre D, Ribeiro PA, Kramer CK, et al. Physical activity advice only or structured exercise training and association with HbA1c levels in type 2 diabetes: a systematic review and meta-analysis. JAMA 2011; 305: 1790-1799.
52. Biessels GJ, Staekenborg S, Brunner E, Brayne C, Scheltens P. Risk of dementia in diabetes mellitus: a systematic review. Lancet Neurol 2006; 5: 64-74.
53. Anstey KJ, Cherbuin N, Budge M, Young J. Body mass index in midlife and late-life as a risk factor for dementia: a meta-analysis of prospective studies. Obes Rev 2011; 12: e426-437.
54. Anstey K, von Sanden C, Salim A, O'Kearney R. Smoking as a risk factor for dementia and cognitive decline: a meta-analysis of prospective studies. Am J Epidemiol 2007; 166: 367-378.
55. Kris-Etherton PM, Harris WS, Appel LJ; American Heart Association, Nutrition Committee. Fish consumption, fish oil, omega-3 fatty acids and cardiovascular disease. Circulation 2002; 106: 2747-2757.
56. Scarmeas N, Stern Y, Mayeux R, Manly JJ, Schupf N, Luchsinger JA. Mediterranean diet and mild cognitive impairment. Arch Neurol 2009; 66: 216-225.
57. Alzheimer's Association. Changing the trajectory of Alzheimer's disease: a national imperative. Washington DC: Alzheimer's Association; 2010.