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Review

Life style interventions to reduce the risk of dementia

Leon Flicker[a,b,*]

[a] Western Australian Centre for Health and Ageing, Centre for Medical Research, Western Australian Institute for Medical Research, Australia
[b] Geriatric Medicine, School of Medicine and Pharmacology, University of Western Australia, Australia

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ABSTRACT

Dementia has often thought to be unavoidable and incurable. In recent years, risk factors, including lifestyle attributes, have been associated with the two commonest forms of dementia, Alzheimer's Disease and vascular dementia. There is also new evidence that the adult brain maintains plasticity and response to external stimuli. Beside considerable observational data of the effect of lifestyle factors there is now increasing empirical evidence that alterations in lifestyle factors may decrease an individual's risk of developing dementia. The evidence is strongest for increasing an individual's level of physical activity, followed by the cessation of smoking. These interventions carry few risks and have many additional health benefits, so can be recommended for most of the older population. Other interventions such as increasing social engagement, cognitive stimulation and homocysteine lowering vitamin supplements also appear promising, with considerable observational evidence supporting their uptake, although there is still a lack of empirical evidence for these interventions.

Contents

1. Introduction

Previously, people with a form of dementia were categorized into two large groups based on the age of onset, i.e. pre-senile and senile forms of the disease. The subsequent demonstration that the commonest pathology found in the brains of people with senile dementia was Alzheimer type pathology called into question this methods of categorization and increasingly older patients were diagnosed as having specific clinical forms of dementia. These include dementia in Alzheimer's Disease (either early or late onset), vascular dementia, and dementia in other diseases, as categorized by the World Health Organization ICD 10 [1]. More recently Dementia with Lewy Bodies is also commonly diagnosed [2]. However, recent neuro-pathological studies of older people who have died with dementia has revealed that 'pure' forms of these disease entities are relatively uncommon and many older people manifest multiple neuro-pathologies which has led to cognitive dysfunction [3]. Therefore it is still reasonable in older people to consider prevention of dementia, rather than individual pathological types.

In addition there has been considerable evidence that mid-life vascular risk factors which make older people prone to cardiovas-

* Correspondence address: Department of Geriatric Medicine, Royal Perth Hospital, Box X2213 GPO, Perth, WA 6001, Australia. Tel.: +61 8 9224 2750; fax: +61 8 9224 2063.
E-mail address: leonflic@cyllene.uwa.edu.au.

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cular outcomes, increase the risk of Alzheimers Disease (AD) [4]. These risk factors have been also assumed to increase the risk of vascular dementia and therefore it is now widely suspected that the control of vascular risk factors will decrease the incidence and progression of the two commonest pathological types of dementia, AD and vascular dementia. At the present time there have been no risk factors identified for the third commonest form of dementia, Dementia with Lewy bodies [2]. It is thus reasonable to consider that lifestyle interventions that decrease the risk of vascular disease may also decrease the risk of dementia.

Another underlying concept by which lifestyle factors may improve cognition is the idea of plasticity. This is summarized as the ability or capacity of the brain to "achieve new functions by transforming its constituent elements and/or its internal connectivity network according to environmental constraints" [5]. These modern concepts challenge the idea that the brain is fully formed and unable to adapt to environmental stimuli and that some stimuli can have benefits even into later life. Thus, it may be possible that environmental manipulation can have brain effects well into old age.

There has been considerable populist enthusiasm for some of these lifestyle interventions, as opposed to others. In particular cognitive stimulation seems to have had considerable support, not matched by the available evidence. This article will deal with the lifestyle interventions based on the order of the strength of evidence and thus will begin with physical activity and smoking cessation before dealing with social networks, cognitive stimulation, dietary factors and alcohol ingestion.

2. Physical activity

There has been substantial work performed exploring the idea of plasticity and brain changes in rodents and this has been recently comprehensively reviewed [5]. Many of the animal studies have been performed in rodents, and it is difficult to equate rodent behavior to a human equivalent, although access to a running wheel approximates the human equivalent of voluntary exercise. Importantly wheel running has been demonstrated to have beneficial effects on rodents not just in their developmental phase, but also in adulthood and senescence. In one experiment the availability of a running wheel was associated with reduction in memory deficits and a decrease in beta amyloid pathology in the hippocampi of transgenic mice [5]. In another experiment, neuroplasticity was demonstrated in adult rats (greater than 6 months of age) who were provided with an available running wheel compared with controls. Capillary growth was demonstrated in the motor cortex and also cerebral perfusion generally increased [5]. These animal experiments provide a biologically plausible basis for the effect of physical activity on the brain of humans.

Besides these animal experiments, there has been considerable observational data collected in humans. Many of these studies were summarized in a review published in 2004 [6]. The authors identified nine reports of longitudinal studies exploring the association between physical activity and the subsequent progression to dementia. The two reports which reported the largest numbers were based on the same study, the Canadian Study of Health and Aging [7,8]. This study and two others, demonstrated that regular and high levels of physical activity are associated with a decreased risk of dementia and AD. Since the publication of that review there have been many further reports demonstrating an inverse association between physical activity with cognitive decline [9–14] and that increased levels of physical activity are associated with a subsequently decreased incidence of dementia [15,16] and vascular dementia [17].

Basic science and observational evidence on humans strongly supports the hypothesis that increased physical activity prevents the onset of dementia. There is now increasing amounts of trial evidence to support this. A recent systematic review [18] summarized 11 randomized control trials (RCTs) published until December 2005. Many of these intervention studies demonstrated an improvement in cardiovascular fitness. Overall an improvement in cognitive function was found in motor function and auditory attention, standardized effect sizes of 1.17 and 0.50, respectively. (Standardized effects are calculated by dividing the difference in mean outcome between groups by the standard deviation of outcome among participants.) Moderate effects were observed for cognitive speed, effect size 0.26, and visual attention, effect size 0.26.

There have been two other recent RCTs. The first examined the effects of aerobic exercise or vitamin B supplementation on cognitive function in older adults with mild cognitive impairment (MCI) [19]. In this study, 152 participants aged 70–80 years were randomly assigned in a two by two factorial design to a moderate-intensity walking program, a daily B vitamin pill or placebo control for 1 year duration. Intention-to-treat analysis revealed no main intervention effects for either intervention at 6 or 12 months, but there were trends for effects in improving memory in men and memory and attention in women with better adherence. A recent large study has produced the most promising results [20]. A total of 170 participants with memory complaints were randomized to a 24-week home-based program of physical activity or control group. Approximately 60% of these subjects had MCI. In an intent-to-treat analysis, participants in the intervention group improved 1.3 points (95% confidence interval, (CI) −2.38 to −0.22) compared to those in the usual care group on the main outcome measure of the Alzheimer Disease Assessment Scale-Cognitive Subscale (ADAS-Cog) score at the completion of the 24-week trial. The ADAS-Cog has a possible range of 0-70, with a mean baseline score in these participants of 7.0. This improvement was maintained for 12 months after the completion of the intervention. Word list delayed recall and Clinical Dementia Rating scale score improved modestly as well.

There are now considerable animal studies and observational human data that physical activity prevents cognitive decline and dementia. There is also recent human trial evidence that increased physical activity has cognitive benefits in older people at risk for dementia. At this stage there are no confirmatory RCTs that increased physical activity prevents dementia.

3. Smoking cessation

Initially smoking was thought to be protective for the development of AD. This was largely based on case control studies which demonstrated an inverse association between smoking and AD. These data were found to be misleading and prone to survivorship bias when compared with cohort studies which have shown a positive association between smoking and AD [21]. A recent comprehensive meta-analysis of prospective studies has found that smoking does indeed increase the risk for AD [22]. Further evidence for a biological basis for this association was produced by a study demonstrating that in older smokers without discernible cognitive changes, there exist abnormalities in the grey matter of the brain almost identical to that found in people with early AD. Smokers were found to have decreased grey matter density in the posterior cingulate and precuneus, right thalamus and frontal cortex compared with non-smokers [23].

There are many proven methods to assist adults to quit smoking including physician advice [24] and nicotine replacement therapy [25]. Although older people have often smoked for in excess of 40 years, there is evidence that a sizeable proportion will respond to smoking cessation programs. In one study in people over the age of 65 years, 25% had ceased smoking at 6 months after attempting to

quit, and at 24 months 24% of this group had not smoked for 30 days [26]. Thus, there are reasonable grounds for optimism in assisting older people to quit smoking. There is as yet no evidence that cessation of smoking will decrease the risk of dementia associated with this habit. However, there are considerable other benefits associated with smoking cessation and therefore this is a simple lifestyle intervention that older people can adopt to potentially reduce their risk of dementia.

4. Social engagement

This is a difficult area for review as definitions of the make-up of the exposures and interventions are inconsistent and vary from study to study. Also, interventions comprising activities to enhance social engagement are problematic to develop and even harder to control for in RCTs as the "social contact" group is often considered to be equivalent to the placebo of drug trials. The area has some particular biases, but the major issue is reverse causality, as those individuals with superior executive functioning may have greater proclivity to social engagement, and such cognitive strength may make the individual less prone to develop dementia.

It has been demonstrated that rodents reared in "enriched" environments have enhanced cognitive abilities in spatial and non-spatial memory tests and enhanced hippocampal neurogenesis [5]. This 'enriched' environment is achieved by raising the rodents in groups and providing toys, tunnels and running wheels. It was initially considered that this effect predominated in the "juvenile" stage of the life cycle of the rodents, but the effects of this enriched environment have been observed to persist into adulthood.

The evidence regarding social engagement preventing dementia in humans is entirely observational and quite heterogenous in type. Fratiglioni et al. [6] summarized seven studies of the association between social networks and cognitive decline and found mixed results. Some studies found no association whereas associations were founds with diverse factors, e.g. social disengagement, emotional support, social and "productive" activities. There were no RCTs regarding social networks and cognition. Six observational studies examined the association between social networks and the onset of dementia, the studies often found diverse associations. E.g. The relationships studied included never married as opposed to number of social contacts or quality of social networks. These methodological shortcomings and others have been summarized in a recent review [27] which reinforces the lack of empirical evidence for social networks in the prevention of dementia.

5. Cognitive stimulation

Cognitive stimulation has also been trialed in attempt to capitalize on the effect of social stimulation. The lack of classification of the diverse approaches utilized has been one of the major difficulties in developing a scientific coherence to this area. One approach, which has considerable face validity, has been separating the interventions into two types. Cognitive training involves guided practice on a set of tasks that reflect particular cognitive functions, such as memory, attention, or problem-solving. This stimulation can be offered individually or in groups. Another more complex approach is cognitive rehabilitation, which involves identification of the individual's needs and goals, and the development of strategies for taking in new information or methods of compensating such as using memory aids. This rehabilitation approach attempts to capitalize on intact domains to help maintain cognition and prevent or delay decline [28].

Using this taxonomy 35 potential studies were identified but only nine were included in a systematic review, all of which used the approach of cognitive training. Importantly this systematic review only included patients who had early or mild dementia. They concluded that there was no evidence of any benefits of cognitive training and no RCTs could be identified for cognitive rehabilitation. The effect of cognitive training on normal older people has also been reviewed [29]. Seven studies were included in the meta-analysis with six of these studies using neuropsychological tests as the main outcomes. There were positive results seen in these studies but the results of these neuropsychological tests in normal older people are difficult to extrapolate to everyday function or to dementia prevention. In one study, the ACTIVE study [30] positive results of cognitive training were observed on extended follow-up of 5 years. This was for the outcome of perceived difficulty on instrumental activities of daily living. However, this was found in only one of three intervention groups and the effect size was small (standardized mean difference 0.29, 99% CI, 0.03–0.55). Although promising, the effects of cognitive training and rehabilitation in older people at risk of dementia remain to be determined in RCTs.

6. Dietary factors

There has been considerable interest in macro- and micronutrient alterations for the prevention of dementia. Interest in macronutrient alterations have focused on the reduction of saturated fat intake or other measures. To my knowledge there are no reported RCTS which have used the intervention of alteration in dietary fats in those older people who are at risk of dementia. The supplementation with omega 3 polyunsaturated fatty acids has also been suggested as a possible intervention for dementia but a systematic review concluded there was no available evidence from RCTs [31]. A recent small RCT involving people with MCI and dementia found a suggestion of some benefits but the study was far from conclusive [32].

Whether the use of supplementary micronutrients is really a lifestyle intervention can be argued but large numbers of older people do ingest these without consulting their physician. Research in micronutrients has concentrated on two hypothesized mechanisms, the anti-oxidant hypothesis, mostly evaluating supplementation with vitamins C and E, and the homocysteine lowering hypothesis which has explored the use of folate, vitamin B_{12} and B_6. A recent review of vitamin E concluded that there was no evidence of efficacy for the prevention of dementia [33]. The fact that high dose vitamins A and E supplementation have been associated with increased mortality [34], suggests that widespread use of these vitamins for the prevention of dementia cannot be supported. The use of supplementary folate supplements, with or without vitamin B_{12}, to prevent cognitive decline has produced conflicting results [35]. There is evidence of benefits for cognition in people with high levels of homocysteine [36] but there is a need for replication and further confirmation on the clinical meaning of these cognitive benefits.

7. Alcohol ingestion

This is a very contentious area. The case for a particular form of dementia associated with excess alcohol ingestion is surprisingly weak [37] and that the cognitive impairment may be due to accompanying insults such as thiamine deficiency, traumatic brain injury, smoking, etc. The cognitive effects of large daily amounts of alcohol per se are difficult to quantify. Coupled with this, low amounts of alcohol ingestion have been found to be protective for the development of dementia. A systematic review of 23 cohort studies [38] concluded that small amounts of alcohol were protective for the development of dementia (risk ratio 0.63; 95% CI 0.53–0.75). Caution should be exercised before advising individuals to ingest more alcohol as these observational studies are prone to bias, particularly

in that those who abstain from alcohol may have already suffered harm from previous excessive alcohol intake.

8. Conclusion

There is increasing evidence that lifestyle interventions can decrease the risk of dementia. Importantly the lifestyle interventions with the strongest evidence, increased physical activity and smoking cessation carry so many additional health benefits that they can now be advocated for all older people. The evidence for cognitive training has largely focused on improvements in performance on cognitive tests in normal older people and whether this produces meaningful improvements in the lives of older people or prevents dementia is uncertain. Increased social engagement has been observed to decrease the risk of dementia but the evidence is entirely observational. The evidence for dietary manipulation and supplementation is largely negative although the use of folate supplementation show some promise and is currently subject to ongoing research. Although the observational evidence for alcohol ingestion is positive, the concerns regarding bias from these studies and the health and social consequences of excessive drinking makes the formulation of public health messages difficult.

Contributors

LF performed the literature search and drafted the manuscript.

Conflicts of Interest

LF has no perceived conflicts of interest.

Provenance

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References

[1] World Health Organization. The ICD-10 Classification of Mental and Behavioural Disorders: Clinical Descriptions and Diagnostic Guidelines. Geneva, Switzerland: World Health Organization; 1992. p. 42–56.
[2] McKeith IG, Dickson DW, Lowe J, et al. Diagnosis and management of dementia with Lewy bodies: third report of the DLB Consortium. Neurology 2005;65:1863–72.
[3] Jellinger KA. Morphologic diagnosis of "vascular dementia"—a critical update. J Neurol Sci 2008;270:1–12.
[4] Craft S. The role of metabolic disorders in Alzheimer disease and vascular dementia: two roads converged. Arch Neurol 2009;66:300–5.
[5] Pietropaolo S, Sun Y, Li R, Brana C, Feldon J, Yee BK. The impact of voluntary exercise on mental health in rodents: a neuroplasticity perspective. Behav Brain Res 2008;192:42–60.
[6] 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.
[7] Laurin D, Verreault R, Lindsay J, MacPherson K, Rockwood K. Physical activity and risk of cognitive impairment and dementia in elderly persons. Arch Neurol 2001;58:498–504.
[8] Lindsay J, Laurin D, Verreault R, et al. Risk factors for Alzheimer's disease: a prospective analysis from the Canadian Study of Health on Aging. Am J Epidemiol 2002;156:445–53.
[9] Yaffe K, Barnes D, Nevitt M, Lui LY, Covinsky K. A prospective study of physical activity and cognitive decline in elderly women who walk. Arch Intern Med 2001;161:1703–8.
[10] Lytle ME, Vander Bilt J, Pandav RS, Dodge HH, Ganguli M. Exercise level and cognitive decline. The MoVIES Project. Alzheimer Dis Assoc Disord 2004;18:57–64.
[11] Van Gelder BM, Tijhuis MA, Kalmijn S, Giampaoli S, Nissinen A, Kromhout D. Physical activity in relation to cognitive decline in elderly men. The FINE Study. Neurology 2004;63:2316–21.
[12] Weuve J, Kang JH, Manson JE, Breteler MM, Ware JH, Grodstein F. Physical activity, including walking and cognitive function in older women. JAMA 2004;292:1454–61.
[13] Almeida OP, Norman P, Hankey G, Jamrozik K, Flicker L. Successful mental health aging: results from a longitudinal study of older Australian men. Am J Geriatr Psychiatry 2006;14:27–35.
[14] Niti M, Yap KB, Kua EH, Tan CH, Ng TP. Physical, social and productive leisure activities, cognitive decline and interaction with APOE-epsilon 4 genotype in Chinese older adults. Int Psychogeriatr 2008;20(April (2)):237–51.
[15] Abbott RD, White LR, Ross GW, Masaki KH, Curb JD, Petrovitch H. Walking and dementia in physically capable elderly men. JAMA 2004;292:1447–53.
[16] Podewils LJ, Guallar E, Kuller LH, et al. Physical activity, APOE genotype, and dementia risk: findings from the Cardiovascular Health Cognition Study. Am J Epidemiol 2005;161:639–51.
[17] Ravaglia G, Forti P, Lucicesare A, et al. Physical activity and dementia risk in the elderly: findings from a prospective Italian study. Neurology 2008;70:1786–94.
[18] Angevaren M, Aufdemkampe G, Verhaar HJJ, Aleman A, Vanhees L. Physical activity and enhanced fitness to improve cognitive function in older people without known cognitive impairment. Cochrane Database Syst Rev 2008;(3), doi:10.1002/14651858.CD005381.pub3. Art. No.: CD005381.
[19] van Uffelen JG, Chinapaw MJ, van Mechelen W, Hopman-Rock M. Walking or vitamin B for cognition in older adults with mild cognitive impairment? A randomised controlled trial. Br J Sports Med 2008;42:344–51.
[20] 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;300:1027–37.
[21] Almeida OP, Hulse GK, Lawrence D, Flicker L. Smoking as a risk factor for Alzheimer's disease: contrasting evidence from a systematic review of case–control and cohort studies. Addiction 2002;97:15–28.
[22] Anstey KJ, 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;66:367–78.
[23] Almeida OP, Garrido GJ, Lautenschlager NT, Hulse GK, Jamrozik K, Flicker L. Smoking is associated with reduced cortical regional gray matter density in brain regions associated with incipient Alzheimer disease. Am J Geriatr Psychiatry 2008;16:92–8.
[24] Stead LF, Bergson G, Lancaster T. Physician advice for smoking cessation. Cochrane Database Syst Rev 2008;(2), doi:0.1002/14651858.CD000165.pub3. Art. No.: CD000165.
[25] Stead LF, Perera R, Bullen C, Mant D, Lancaster T. Nicotine replacement therapy for smoking cessation. Cochrane Database Syst Rev 2008;(1), doi:10.1002/14651858.CD000146.pub3. Art. No.: CD000146.
[26] Tait RJ, Hulse GK, Waterreus A, Flicker L, Lautenschlager NT, Jamrozik K, et al. Two-year outcomes from a cessation of smoking intervention in older adults. J Smok Cessat 2008;3:101–9.
[27] Coley N, Andrieu S, Gardette V, et al. Dementia prevention: methodological explanations for inconsistent results. Epidemiol Rev 2008;30:35–66.
[28] Clare L, Woods B. Cognitive rehabilitation and cognitive training for early-stage Alzheimer's disease and vascular dementia. Cochrane Database Syst Rev 2003;(4), doi:10.1002/14651858.CD003260. Art. No.: CD003260.
[29] 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;17:179–87.
[30] Willis SL, Tennstedt SL, Marsiske M, et al. Long-term effects of cognitive training on everyday functional outcomes in older adults. JAMA 2006;296:2805–14.
[31] Lim WS, Gammack JK, Van Niekerk JK, Dangour A. Omega 3 fatty acid for the prevention of dementia. Cochrane Database Syst Rev 2006;(1), doi:10.1002/14651858.CD005379.pub2. Art. No.: CD005379.
[32] Chiu CC, Su KP, Cheng TC, et al. The effects of omega-3 fatty acids monotherapy in Alzheimer's disease and mild cognitive impairment: a preliminary randomized double-blind placebo-controlled study. Prog Neuropsychopharmacol Biol Psychiatry 2008;32:1538–44.
[33] Isaac MGEKN, Quinn R, Tabet N. Vitamin E for Alzheimer's disease and mild cognitive impairment. Cochrane Database Syst Rev 2008;(3), doi:10.1002/14651858.CD002854.pub2. Art. No.: CD002854.
[34] Bjelakovic G, Nikolova D, Gluud LL, Simonetti RG, Gluud C. Mortality in randomized trials of antioxidant supplements for primary and secondary prevention: systematic review and meta-analysis. JAMA 2007;297:842–57.
[35] Malouf R, Grimley Evans J. Folic acid with or without vitamin B12 for the prevention and treatment of healthy elderly and demented people. Cochrane Database Syst Rev 2008;(4), doi:10.1002/14651858.CD004514.pub2. Art. No.: CD004514.
[36] Durga J, Van Boxtel MPV, Schouten EG, Kok FJ, Katan MB, Verhoef P. Effect of 3-year folic acid supplementation on cognition function in older adults in the FACIT trial a randomized double blind controlled trial. Lancet 2007;369:208–16.
[37] Hulse GK, Lautenschlager NT, Tait RJ, Almeida OP. Dementia associated with alcohol and other drug use. Int Psychogeriatr 2005;17(Suppl. 1):S109–27.
[38] Peters R, Peters J, Warner J, Beckett N, Bulpitt C. Alcohol, dementia and cognitive decline in the elderly: a systematic review. Age Ageing 2008;37:505–12.