Modifiable Lifestyle Risk Factors for Alzheimer’s Disease

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Abstract. There is increasing evidence that some lifestyle factors are linked to the development of Alzheimer’s disease. Many of these are potentially modifiable and include smoking, physical activity, education, social engagement, cognitive stimulation, and diet. Modification of most of these factors has other health advantages, increasing the potential benefits of modifying the individual’s lifestyle. Unfortunately, most of the current evidence is based on observational data, and where human trials have been performed they have used surrogate outcomes rather than the development of Alzheimer’s disease. For many of these modifiable lifestyle factors, such trials may never be performed, and an individual’s choice may need to be based on the available evidence.

Keywords: Alzheimer’s disease, lifestyle, older people, prevention

MODIFIABLE VERSUS NON-MODIFIABLE

The major proven risk factors for Alzheimer’s disease (AD) remain advancing age and family history. Both these factors are irreversible and for many years supported nihilistic attitudes in the prevention of AD. More recently, animal and observational human data have suggested that environmental factors, including lifestyle factors, may alter the risk of AD and a ‘prudent’ lifestyle may prevent AD. Fortunately many of these factors seem to decrease the risk of other major causes of morbidity and mortality in aging populations, increasing the impetus to recommend such lifestyle choices for everyone. Unfortunately, the evidence for these lifestyle interventions, although promising, is not based on human trials, but largely on observational data, i.e., comparing the rate of AD or cognitive decline in older people who choose that lifestyle factor and those who do not. Where trials have been performed, surrogate outcomes have been used, rather than the incidence of AD. For many of these factors, it is unlikely that randomized trials will be performed, and decisions about lifestyle interventions will be guided by the available data. However, in the presence of global aging, where the most dramatic increases in the number of people with AD will occur in the developing world [1], these relatively simple lifestyle choices have the potential to reduce the total burden of AD by a considerable amount.

SMOKING

For many years smoking was considered to be protective for the development of AD. It had been postulated that acute stimulation of neuronal nicotinic receptors may have beneficial effects on people with AD [2] and that prolonged administration may have further benefits and increase neuronal survival by unknown mechanisms [3]. Reviews of case control studies had demonstrated that smoking was associated with a decreased
Smoking is clearly a modifiable risk factor although some have argued that for older people, it is too late to quit smoking. There are many proven methods to assist adults to quit smoking including physician advice [10] and nicotine replacement therapy [11]. A sizeable proportion of older people will quit in response to smoking cessation programs. In one study in smokers 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 [12].

**PHYSICAL ACTIVITY**

There are now considerable data on the persistence of brain plasticity into late adulthood. Work in rodents has demonstrated that provision of a running wheel to encourage exercise was associated with reduction in memory deficits and a decrease in amyloid-\(\beta\) pathology in the hippocampi of transgenic mice [13]. In another experiment, capillary growth was demonstrated in the motor cortex and cerebral perfusion also generally increased [13]. These types of experiments provide a biological plausibility for cognitive benefits of physical activity.

Over the last decade there have been many reports of prospective studies of the association between physical activity and risk of dementia. These studies have recently been reviewed, and this systematic review included 16 studies, two of which examined the effect of physical activity on Parkinson's disease [14]. The remaining 14 studies, which examined the outcomes of dementia and AD, contained data on 27,255 participants of which 2731 had a diagnosis of dementia or AD. The pooled relative risk for overall dementia in the highest physical activity category compared with the lowest was 0.72 (95% CI 0.60–0.86), and for AD 0.55 (95% CI 0.36–0.84). In support of these findings, another 10 studies reported the effects of physical activity on cognitive performance but not for the outcome of dementia. These studies also largely supported a positive effect of physical activity on cognitive performance over time. However, since that systematic review, a recent study only found a protective effect of physical activity for the outcome of vascular dementia and not AD [15]. Overall these results seem reasonably consistent, but there is the possibility that reverse causality is occurring; those people who are in better cognitive health or with increased cognitive reserve may choose greater levels of physical activity. To avoid such biases randomized study designs are preferable.
Ideally trials of increased physical activity should be examined against the outcome of incident AD. Unfortunately such trials have not yet been performed. Such studies would need a large number of subjects even if the participants were selected to be at high risk of AD. Instead, a diverse range of cognitive outcomes have been evaluated in individuals at varying risk of subsequent decline. There have also utilized quite different methods for increasing the physical activity of their subjects. A recent systematic review [16] summarized 11 randomized control trials (RCTs) published up to December 2005. One of the selection criteria for this review was that the interventions should be directed at improving aerobic fitness. It is not clear from our present state of understanding that any effect of increased physical activity can only be ascribed to aerobic fitness as opposed to say strength. Many of the included intervention studies did demonstrate an improvement in cardiovascular fitness. Overall an improvement in cognitive function was found in motor function and auditory attention, weighted mean difference of 1.17 (95% CI 0.19–2.15) and 0.52 (95% CI 0.13–0.91), respectively. Moderate effects were observed for cognitive speed, standardized mean difference of 0.26 (95% CI 0.04 to 0.48), and visual attention, standardized mean difference of 0.26 (95% CI 0.02–0.49). The reviewers rightly criticized the lack of consensus on what were the most appropriate measurement tools to determine an effect as well as the short term nature of the trials which on average was 14 weeks. Although there were trends favoring the exercise groups, there were no definitive effects on memory or executive functioning.

There have been several other recent RCTs. They include a study of the effects of aerobic exercise or vitamin B supplementation on cognitive function in older adults with mild cognitive impairment (MCI) [17]. In this study, 152 participants aged 70 to 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 one year duration. Intention-to-treat analysis revealed no main intervention effects for either intervention at six or 12 months, but there were trends for effects in improving memory in men and memory and attention in women with better adherence. Similarly in a pilot study of moderate intense physical activity on cognitive outcomes, there were no major between groups differences [18]. However, there were intriguing correlations between changes in physical activity and cognitive scores, particularly for attentional tasks. Another study has produced even more promising results [19]. In this study, based in Perth, Australia, 170 participants with memory complaints were randomized to a 24-week home-based program of physical activity or control group. The physical activity program was relatively non-specific. 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. This improvement was maintained for 12 months after the completion of the intervention, although the overall effect size of the intervention was limited. The word list delayed recall test (a test of memory) and Clinical Dementia Rating scale score improved modestly as well, despite all the subjects commencing in the non-dementia range. Unfortunately, this study was not sufficiently large to determine any effect on the incidence of dementia. Another moderately large positive study has added further complexity to these issues [20]. This study used progressive resistance training as the intervention in a graded fashion. They found cognitive benefits of training designed to increase strength as opposed to aerobic ability.

There is increasing evidence that increasing physical activity, an easily modifiable lifestyle choice, has cognitive benefits in older people. There is a large amount of observational data, virtually all of which is consistent with this premise. There is an increasing amount of good quality trial data, but unfortunately not with incidence of AD as an outcome. Unfortunately it is not clear what type of intervention and for whom physical activity would have the most benefit. Nevertheless the amount of evidence is encouraging in guiding those people who wish to avoid cognitive decline.

EDUCATION

There are a considerable numbers of studies that have addressed the effect of education on cognitive decline and the incidence of dementia. Six well performed studies found an inverse relationship between level of education and incidence of dementia [21]. However, the causal pathway for this association is not clear. Recent observational data have arisen from cohort studies with multiple time points in attempt to tease out the effects of confounding due to detection bias. This is likely to occur because the more highly educated members of the cohort are less likely to be detected as having de-
developed cognitive impairment. For this reason it may be preferable to use cognitive changes over time as the outcome measure. In a systematic review published in 2000 [22], 14 studies were indentified which included two time points to measure cognitive changes in older people. A descriptive synthesis of these studies noted that higher levels of education seemed to be associated with a less rapid decline in cognitive functioning. The type of tests appeared to influence these results with those studies examining crystallized intelligence showing greater protective effects than those which examined aspects of fluid intelligence.

However, more recent studies have found different effects. One study based on the Cambridge City over 75s Cohort. [23] employed simultaneous adjustment for the effects of missing values and other demographic variables based on the multiple time points of the study. After such adjustment, education was no longer predictive of subsequent cognitive decline but did predict better scores on the MMSE. These findings are similar to a study based on the Chicago Health and Aging Project [24]. In that study, over 6000 participants were followed for an average of three interviews. By using a series of mixed effects models, they were firstly able to confirm that a higher level of education was associated with a higher level of baseline cognition, but education did not affect the rate of decline in cognition.

There are several possibilities for the effects of education. Firstly education may just be confounded with other factors associated with higher socio-economic status such as diet and physical activity, or even more cognitively stimulating activities in later life and these factors exert these putative effects. Secondly, higher levels of education make it more difficult to diagnose cognitive impairment/decline, a form of ascertainment bias. Thirdly, higher levels of education lead to greater cognitive reserve, which is supported by twin models [25]. This increased reserve may operate on a basic neuronal level or just increase coping resources based on similar neuronal structures. Fourthly, it has been demonstrated that cognitive activity results in an increase in regional cerebral blood flow and this may provide an increased vascular “reserve” for individuals as they age [26]. At this stage, it appears likely that greater levels of education either decrease the overall risk of AD or delay the apparent onset.

SOCIAL ENGAGEMENT

There is a concept that social engagement is a form of neural stimulation based on the equivalent of an enriched environment for rodents. An ‘enriched’ environment for rodents is achieved by raising the rodents in groups and providing toys, tunnels, and running wheels. This produces enhanced cognitive abilities in spatial and non-spatial memory tests and hippocampal neurogenesis [13]. The term “social engagement” is imprecise, and it has been difficult to define whether it is the quantity or quality of the social relationships that is important. As disturbance in social functioning forms part of the definition of dementia, there is always the possibility that the arguments are circular and that a lack of social engagement represents one of the early signs of dementia. On the whole the evidence for social engagement preventing AD in humans is entirely observational.

Fratiglioni and colleagues [27] summarized seven studies of the association between social networks and cognitive decline. There were diverse findings; some studies found no association whereas other studies found associations with a multitude of factors, e.g., social disengagement, emotional support, and social and “productive” activities. Six studies examined the association between social networks and the onset of dementia, and these studies also found variable associations. For example, the relationships studied included never married as opposed to number of social contacts or quality of social networks. Reverse causality is a problem in this area as those individuals with lifelong superior executive functioning may be more likely to have developed social activities, and such cognitive abilities may make the individual less prone to develop cognitive decline or be detected as having dementia.

Recent work based on the Honolulu-Asia Aging Study would tend to support the hypothesis that a lack of social engagement may be an early sign of dementia and AD [28]. In that study levels of social engagement were based on a composite score of marital status, living arrangements, participation in social, political, or community groups, participation in social events with coworkers or friends, and the existence of a confidant. In late life, compared with reference level of highest quartile of late-life social engagement, those in the lowest quartile had an increased risk of dementia, with a hazard ratio of 2.34 (95% CI 1.18–4.65). However, there was no evidence that the level of social engagement in mid-life predicted an increased risk of dementia. There was a trend of increasing dementia risk with decreasing late-life social engagement. Findings were similar with the subtypes of dementia, AD, or vascular dementia. These findings would imply that the change in level of social engagement is predictive of AD rather
than the lifelong level of social engagement. This has important implications as to whether social engagement has any real effect but also the timing of any intervention, which on the basis of this study, should occur in later life.

The inherent difficulties in measurement of, and interventions in, social engagement make this a very difficult area to study. There is as yet no clear consensus what are the domains of this measure and how do we determine this. Trials to intervene in social engagement are difficult to develop, and it is extremely difficult to determine to what the control group should be exposed. The “social contact” group is often considered to be equivalent to the placebo group, but in these types of studies, any social contact may from part of the intervention.

COGNITIVE STIMULATION

Cognitive stimulation has also been loosely based on the idea of plasticity of the human brain well into adulthood and that these activities correspond to an “enriched” environment. The types of activities involved with cognitive stimulation have been divided into two major types, cognitive training and cognitive rehabilitation. 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. Cognitive rehabilitation is more complex and involves identification of the individual’s needs and goals. By definition it implies that there are already identified cognitive deficits and that strategies can be developed to overcome these deficits or by compensating for them by using external mechanisms such as memory aids. The rehabilitation approach attempts to capitalize on intact domains to help maintain cognition and prevent or delay decline [29]. There has been a review of these strategies in people with dementia [29], but there is no evidence of efficacy. There are a few studies of this time intensive approach on people who do not already fulfill criteria for dementia. Not unexpectedly, there have been a few reports of this technique used in subjects with amnestic MCI [30]. The approach looks promising on the effects on memory tests but the studies have not had sufficient power to detect an effect on conversion rates to dementia from MCI, nor an effect on everyday living tasks. For example in one study [31] of 54 participants, there seemed to be some positive effects on self-reported memory functioning but no objective findings of functional improvements.

The effect of cognitive training on normal older people has also been reviewed [32]. 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 essentially these are confined to improvements in specific neuropsychological testing based partly on the type of training provided. These findings are difficult to extrapolate to everyday function or to dementia prevention. The exception was in one study, the ACTIVE study [33], where positive results of cognitive training were observed on extended follow-up of five 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). A later report [34] described three different types of variable responders to this form of memory training, raising the intriguing possibility of tailoring cognitive stimulation strategies as to predicted response as opposed to the previously identified deficits (which is essentially the rehabilitation approach).

A recent program which is difficult to categorize is the description of a multimodal cognitive activity program [35]. The intervention was based on training older people to work in teams to help elementary school children learn in the classroom environment. There were two parts to the intervention, an intensive preparatory training course and senior service over the ensuing year. Compared to the randomized controls, the intervention group demonstrated improvements on tasks of executive functioning at follow-up between 4 and 8 months in duration. This study needs to be replicated with a larger sample but may in part be effective due to its multi-modal character, combining the effects of cognitive stimulation increased physical activity and social engagement.

ALCOHOL

It has long been assumed that excessive alcohol ingestion predisposes people to dementia. There is in fact a dearth of good quality data to support this idea. It is not clear as to whether alcohol is itself responsible for major cognitive decline or whether this in fact due to accompanying insults such as thiamine deficiency, traumatic brain injury, strokes, and smoking, which are commonplace for those people who drink excessively.
The cognitive effects of large daily amounts of alcohol per se are difficult to quantify [36]. However for a variety of other medical and in particular social consequences, excessive alcohol intake should be avoided. In terms of availability and in price relative to income, alcohol has become much more readily available over the past two decades in most economically developed countries [37]. Guidelines have become increasingly restrictive, mainly responding to known risks, and limiting men and women to no more than two standard drinks of alcohol per day, even if drunk every day, minimizes any health or social consequences [38]. For healthy men and women, drinking no more than four standard drinks on a single occasion reduces the risk of alcohol-related injury arising from that occasion [38]. For countries [37]. Guidelines have become increasingly restrictive, mainly responding to known risks, and limiting men and women to no more than two standard drinks of alcohol per day, even if drunk every day, minimizes any health or social consequences [38]. For healthy men and women, drinking no more than four standard drinks on a single occasion reduces the risk of alcohol-related injury arising from that occasion [38]. For men and women, drinking no more than four standard drinks on a single occasion reduces the risk of alcohol-related injury arising from that occasion [38]. For men and women, drinking no more than four standard drinks on a single occasion reduces the risk of alcohol-related injury arising from that occasion [38].

For men and women, drinking no more than four standard drinks on a single occasion reduces the risk of alcohol-related injury arising from that occasion [38]. These limits are probably well below the level of alcohol intake which may produce cognitive problems.

Against this backdrop, low amounts of alcohol ingestion have been found to be protective for the development of dementia in observational studies. The mechanism for this observation is unknown. Alcohol is thought to have favorable effects on lipid metabolism, reduced insulin resistance, improved endothelial function, and decreased platelet aggregation [39]. Specific forms of alcoholic beverages, such as red wine, may have additional benefits due to a mixture of polyphenol compounds, including resveratrol [40]. A systematic review of 23 cohort studies [41] concluded that small amounts of alcohol were protective for the development of dementia. The risk ratios associated with alcohol intake for each of the four outcomes were dementia 0.63 (95% CI 0.53–0.75), AD 0.57 (95% CI 0.44–0.74), vascular dementia 0.82 (95% CI 0.50–1.35), and cognitive decline 0.89 (95% CI 0.67–1.17), respectively. The reference category for nearly all these studies was “never drinkers” which has raised concerns regarding bias. Those who abstain from alcohol may have already suffered harm from previous excessive alcohol intake, and may partly explain their elevation of risk of diverse outcomes.

The current guidelines regarding excessive alcohol intake are probably more than adequate to restrict adults to levels of intake which are not associated with cognitive problems. The minimal dose of alcohol which provides “protection” from AD is probably less than an average of one standard drink per day. On account of the known harmful effects of excessive alcohol ingestion, it is unwise to advocate taking daily drinking for these benefits, but equally, there is no reason why those individuals who are drinking within current limits based on the available guidelines should not continue to do so.

**DIETARY FACTORS**

**Micronutrients**

There have been two major avenues of research in micronutrients. The first is in regards to the homocysteine (Hcy) hypothesis. Hcy is a toxic by-product of amino acid metabolism which can in turn be metabolized by pathways facilitated by B vitamins. Elevated total plasma Hcy has been implicated as a possible risk factor for cognitive impairment and dementia [42]. For nine selected case control studies, the standardized mean difference of Hcy levels between AD patients and controls was 1.04 (95% CI: 0.44–1.63), indicating higher Hcy levels in people with AD. Reverse causality may be a particular problem in nutritional studies where people with AD may modify their nutritional intake because of the presence of dementia. For this reason, cohort studies with a prolonged follow-up are preferred so as to evaluate risk factors well away from the development of dementia. For three cohort studies, the presence of hyperhomocysteinemia was associated with a pooled relative risk for AD of 2.5 (95% CI: 1.38–4.56). It is known that oral supplementation with folate, and vitamins B12 and B6, reduces Hcy levels considerably, particularly in those with B12 deficiency or hyperhomocysteinemia [43]. There are no trials which have addressed the question of prevention of AD by the use of B vitamin supplements. Trials which have used cognitive changes as an endpoint have produced conflicting results [44] but in at least one study there is evidence of benefits for cognition in people with high levels of Hcy [45]. There is a need for replication and further confirmation on the clinical meaning of these cognitive benefits.

The other micronutrient hypothesis that has received considerable attention has been concerning antioxidants. This work has focused on the intake of vitamins C and E in food and evaluation of supplementation with these vitamins. A review of antioxidant vitamins has found some conflicting results [46]. In general, cohort studies examining the effects of dietary antioxidants have found a lower risk of cognitive decline and dementia with increasing levels. However, supplementation with these vitamins has not been associated with the same protective effects. The evidence from trials of antioxidants is less favorable. A recent review of vitamin E concluded that there was no evidence of efficacy for the prevention of dementia [47]. The fact that high dose vitamins A and E supplementation have been associated with increased mortality [48] suggests that...
widespread use of supplements of these vitamins for the prevention of dementia cannot be supported. However, a varied diet, which does include these micronutrients, may have some benefit.

**Macronutrients**

Interest in macronutrient alterations have largely focused on the balance of the intake of saturated and unsaturated fatty acids. The unsaturated fatty acids can be further broken down into the monounsaturated fatty acids (such as in olive oil) or the polyunsaturated fatty acids, which are further divided into the n-6 class (largely vegetable oils) and the n-3 class (largely in fish oils). The available observational evidence regarding type and amounts of fatty acids and development of dementia or AD appears inconsistent [46]. Twelve cohort studies were reviewed and there appeared to be in association of high dietary intakes of saturated fats with an increased risk of AD. High intakes of polyunsaturated and monounsaturated fats were protective against cognitive decline. Fish consumption (with increased n-3 polyunsaturated fatty acid consumption) may be associated with a lower risk.

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 [49]. A recent small RCT involving people with MCI and dementia found a suggestion of some benefits but the study was far from conclusive [50].

Another dietary variation that has been studied is the Mediterranean diet. This is based on the understanding that it is the combination of different food components which may be important to prevent AD. These include high intake of vegetables, fruits, and cereals; high intake of unsaturated fatty acids, low intake of saturated fatty acids; a moderately high intake of fish; a low-to-moderate intake of dairy products; a low intake of meat and poultry; and a regular but moderate amount of alcohol [51]. In one study, a Mediterranean diet score was inversely associated with the risk of AD, hazard ratio, 0.91 (95% CI: 0.83–0.98) [51]. These results need to be replicated in other cohorts and there are no trials of Mediterranean diet as an intervention.

**CONCLUSIONS**

There is increasing evidence that some modifiable risk factors may help prevent AD. The evidence is strongest for smoking cessation and increasing physical activity, but the type of physical activity and for whom this might have the greatest benefit is unclear. Education and cognitive stimulation seem to have benefits as well but the evidence is less clear cut. Too much alcohol intake may be deleterious but modest amounts of alcohol intake may be protective for AD. There is emerging evidence that some dietary factors may be important, but interventions to date have been disappointing. The evidence regarding social engagement in the protection of AD is inconsistent.

**DISCLOSURE STATEMENT**

The author’s disclosure is available online (http://www.j-alz.com/disclosures/view.php?id=291).

**REFERENCES**


