Strategies to reduce the risk of cognitive decline and dementia

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The aim of this review is to present factors that are relevant to cognitive decline and risk of dementia in later life. With longer life expectancy, the likelihood of experiencing age-related cognitive difficulties has increased. Maintaining normal cognitive function is necessary for successful performance of activities of daily living and independence in later life. Although cognitive decline and dementia are sometimes unavoidable, there are ways in which people can modify their risk of these outcomes. Furthermore, the authors suggest that factors contributing to deviations from homeostasis may have adverse effects on brain health and possibly increase the risk of cognitive decline and dementia.

Cognitive decline and dementia are commonly cited as being among the most feared age-related problems. People often think of memory lapses and other common cognitive difficulties as signs of oncoming Alzheimer's disease (AD), the most common type of dementia. AD is diagnosed based on the presence of both impairment in multiple cognitive domains and impairment in everyday functioning [1].

Longer life and the aging of the baby boom generation have brought the prevention of cognitive decline and impairment into the center of discussions on improving wellbeing in old age. After several decades of focus on maintenance of physical fitness as a way to slow the aging process, cognitive fitness is also becoming a significant public concern. How common are cognitive problems? In recent studies, 22–56% of community-dwelling older adults expressed memory complaints and the expression 'having a senior moment' has now become part of colloquial language [2]. Adequate cognitive functioning is crucial for successful performance of activities of daily living and, hence, for maintaining independence during older adulthood.

The identification and implementation of strategies to prevent or postpone cognitive decline and AD has important implications for future nursing home usage, healthcare costs, reducing the burden of care giving, increasing wellbeing in old age, and generally helping to conserve societal and personal resources. The aim of this review is to present factors that may influence risk of cognitive decline and/or AD, and to review some of the available preventive strategies. The article will specifically focus on factors thought to be related to the maintenance of normal cognitive function in older

adults and review the research on cognitive training, exercise and physical health, diet and nutrition, medication, and mental health. Although other factors may also be related to cognition, the authors found the reviewed factors to be most relevant.

The concept of cognitive reserve

One possible explanation as to why some older adults remain cognitively intact while others have impaired cognitive function is the reserve hypothesis. According to this hypothesis, individual differences in cognitive abilities are linked to underlying differences in the brain and/or the ability to compensate for age-related neuronal damage by superior problem-solving strategies [3]. The characteristics of one's neural substrate, and the ability to use compensatory strategies as the reserve becomes depleted, may determine when, or if an individual will become cognitively impaired. It is widely believed that a combination of genetic and environmental factors are involved in determining the risk of cognitive impairment in older adulthood.

Genetics

Genetic factors determine approximately 40–80% of cognitive performance [4], with genetic influence declining somewhat in very old age [5]. Family history and genetic predisposition also play important roles in the risk of developing Alzheimer's disease [6]. In particular, the apolipoprotein E (APOE)-ε4 allele has been identified as a risk factor for late-onset AD [7]. In contrast, findings from a recent meta-analysis indicate that the role of APOE-ε4 in normal age-related decline in cognitive functioning is relatively small [8]. Although genetic factors are an important foundation of

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cognitive resources, there may be modifiable environmental factors that would suggest possible strategies to maintain the existing cognitive reserve and reduce risk of cognitive impairment.

Early-life factors

Individual differences in childhood cognitive ability have been identified as strong predictors of late-life cognitive functioning [9,10] and risk of dementia [11]. The socioeconomic position of parents was also found to be associated with adult cognitive function, where lower position is related to poorer adult cognitive function after controlling for age and education [12]. In addition, having fewer siblings and growing up in the suburbs as opposed to an urban area, were found to be associated with lower risk for AD [13]. These factors reflect socioeconomic influences on brain development that may impact the extent of cognitive reserve during formative years and beyond.

The relationship between educational attainment and risk of cognitive impairment and dementia has been widely studied. A longer education is associated with better cognitive functioning in middle and late adulthood [10], and decreased risk of dementia or AD [14,11]. Some researchers suggest that the effect of education can be explained by differences in early-life development (e.g., socioeconomic status), mid-life influences such as occupational exposure or lifestyle [15], or by diagnostic bias, where less educated individuals may show cognitive deficits but not the functional deficits that are typical of AD [16].

Mid-life factors

A growing number of studies report that engaging in leisure activities may promote normal cognitive function [17] and reduce the risk of AD [18]. Findings also suggest that more complex occupations may facilitate intellectual flexibility [19] and can reduce the risk of AD [20]. Occupational and leisure activities may provide a source of continued intellectual stimulation, supporting maintenance of cognitive reserve [21].

Engagement in leisure activities has been found to slow cognitive decline [17,22]. Specifically, greater intellectual, social and physical activity has been found to reduce the risk of dementia and AD [23], whether the activity was measured in old age [24] or mid-life [25]. Alternatively, the protective effect of leisure activity against AD may occur as a function of stress reduction and improved vascular health,

explaining why reduced risk of AD has also been linked to greater engagement in social and physical activities [23]. Others caution that empirical support for a causal link between intellectual stimulation and cognition in older adulthood is still only tentative at best [26,27]. Moreover, intelligence and education, which often determine what type of occupational or leisure activities one pursues, may mediate the relationship. Intervention studies with older adults may better capture any direct effects of intellectual stimulation on cognitive functioning.

Cognitive training

A large number of cognitive training studies with nondemented older adults have been published in recent years. These studies draw on the findings that an intellectually stimulating lifestyle may slow cognitive decline and reduce the risk of cognitive impairment. Neuronal structures appear to respond positively to stimulating experiences, even in old age [28–30].

Recently, cognitive training was examined in a randomized controlled study of almost 3000 volunteers from six metropolitan areas in the USA – the Advanced Cognitive Training for Independent and Vital Elderly (ACTIVE) trial [31]. Participants were randomly assigned to either a no-contact control group or one of three cognitive intervention groups: memory, reasoning or speed of processing. Interventions involved ten training sessions as well as additional booster sessions for a randomly selected subset of participants. The results indicated significant benefits of training in all three cognitive domains compared with the control group. In addition, the benefits of training were maintained at a 2-year follow-up.

A number of studies have focused exclusively on memory training with older adults. Findings from memory training studies suggest that using various mnemonic strategies, whether self-taught [32] or administered by trained group leaders [31], may result in superior memory performance compared with control groups. There is some evidence to suggest that group- and individually-supervised programs are as effective as self-administered, commercially available programs [32], potentially providing an easily available method for cognitive intervention. The benefits of memory training have been found for specific areas such as word list recall, text recall, name recall and name–face memory. Some benefit of memory training also comes in the form of improved confidence in

one's memory functioning [33]. Cognitive restructuring that is focused on encouraging positive beliefs and behaviors about memory function has also been found to improve performance in objective memory tests [34].

The benefit of cognitive training on laboratory-based test performance and subjective memory ability appears to be well established. However, less is known about whether and how these improved cognitive skills help aging individuals in everyday life. The improvement may be restricted to the targeted cognitive domain that was being trained, such as memory, and evidence of transfer of the trained skills to everyday tasks has been limited [35]. For example, in the ACTIVE trial, the authors found significant benefits of cognitive training on the targeted cognitive domains but no significant improvement in everyday cognitive abilities of the trained participants compared with the control group [31]. The lack of transfer to daily activities may have been due to ceiling effects on the measure of everyday cognitive function in this well-functioning sample of participants; however, there is currently little evidence to suggest that memory training can postpone the onset of AD [36].

Physical exercise

Although research is still limited, literature reviews indicate that physical exercise and fitness have a positive influence on memory and cognition, with the most obvious explanation for this association being better vascular health in more physically active individuals [28,37]. Recently, regular physical activity [38] and physical activity in midlife [39] were found to be associated with a reduced risk of AD. It appears that aerobic exercise and cardiovascular fitness could lead to improved vascularization of essential brain structures, thereby facilitating a pattern of neuronal activation in older adults that resembles the pattern found in young adults [37]. Cardiovascular fitness also has been associated with a reduction in age-related loss of brain tissue density in the frontal, parietal and temporal cortices [40], thus potentially reducing the risk of cognitive impairment. Particularly encouraging is the finding that executive function and working memory, two cognitive domains that seem to invariably decline with age and have been implicated in cognitive decline [41] and AD [42], appear most responsive to cardiovascular fitness [28,37,43].

Not all studies have found an association between exercise and cognition. It appears that the cognitive benefits of exercise may be most specific to aerobic activity, which would best facilitate the health of cerebral vasculature [28]. However, it is possible that physical activity could also be beneficial for cognition as a function of stress reduction [28]. In addition, physical activity may ameliorate vascular risk factors such as blood lipid and glucose levels and hypertension, all of which have been associated with the risk of AD [44]. While a certain level of intensity of exercise appears to be desirable in order to observe a direct effect of exercise on cognition, findings from a recent review suggest that engaging in exercise that leads to dehydration and depletion of energy storage may impair cognitive function [45].

Physical health

There is evidence that vascular disease, diabetes and associated factors, such as high blood pressure, high blood glucose and elevated cortisol, may also be risk factors for age-related cognitive decline and AD. Management of these conditions, therefore, may be important for both physical and cognitive health in aging individuals.

Hypertension, a well-established risk factor for stroke, has been linked to cognitive decline [46]. Mid-life hypertension may also be a risk factor for AD [47]. It appears that the same mechanism that underlies an increase in the risk of stroke among hypertensive patients may predispose them to neuronal damage and difficulties with memory and cognition. Hypertension can reduce overall cerebral blood flow, damage major cerebral arteries (thus compromising the blood–brain barrier), reduce the ability of neurons to use glucose to obtain energy and impair neuronal transmission [46].

While a great deal of evidence links high blood pressure to the risk of cognitive impairment, some evidence suggests that low blood pressure has a similar effect on cognitive function and may also increase the risk of AD [48]. This finding implies that the relationship between blood pressure and cognitive impairment may be U-shaped rather than linear. Particularly interesting evidence comes from a recent study where hypotension was related to an increased risk of dementia among individuals over 75 years of age who were followed for an average of 21 years [49]. Alternatively, hypotension in later life may simply reflect physiological damage related to prior high blood pressure and heart disease.

Type 2 diabetes mellitus, which tends to have adult onset and involves reduced sensitivity to insulin and subsequent elevated levels of blood glucose (hyperglycemia), has been associated with cognitive decline and AD [50], and with vascular cognitive impairment [51] in some preliminary studies. Additional evidence regarding the diabetes–dementia association comes from a study where dementia was assessed three decades after the assessment of diabetes [52]. Poorly controlled diabetes may affect cognition by reducing glucose tolerance and insulin resistance, potentially leading to cardiovascular problems, deficits in neurotransmitter function and increased oxidative stress [53].

However, low blood glucose, somewhat more common in insulin-treated, Type 1 diabetes, may also impair cognitive function. For example, hypoglycemia led to poor memory performance in a study with healthy volunteers [54], with the deficits being most pronounced for working memory and delayed recall. The cortex and the hippocampus – a brain structure largely responsible for learning and consolidation of short-term memory – appear to be particularly susceptible to malfunction or damage due to low blood glucose levels [55].

Diet & nutrition

It has been known for decades that nutritional factors can modify the risk of diseases such as heart disease and cancer. More recently, the relationship between nutrition and cognitive functioning has become an important research topic. It is known that healthy functioning of the central nervous system is largely influenced by the availability of essential nutrients [56]. Therefore, although many issues regarding proper diet for cognitive health remain to be addressed, it is clear that nutrition and diet could theoretically affect cognition and the risk of AD.

Deficiencies in folic acid and vitamin B₁₂, which affect up to 15% of the elderly [57], may result in poor cognitive performance [58] and even AD [59]. Two mechanisms have been proposed to explain why this deficiency may affect cognition [58]. A direct mechanism relates to the possibility that low levels of folic acid and vitamin B₁₂ inhibit production of essential neurotransmitters such as dopamine, norepinephrine and serotonin. A second more indirect mechanism involves the role of folic acid and vitamin B₁₂ in decreasing blood concentrations of homocysteine (an amino acid), which is elevated in AD patients [59].

Cholesterol, a by-product of fat metabolism, seems to have a similar indirect influence on memory, whereby cholesterol-related damage to the blood vessels may result in poorer brain health [60] and an increased risk of AD, although cholesterol levels may actually decline at the time of dementia onset [61]. In addition, treatment with cholesterol-lowering drugs has been found to be associated with a reduced risk of cognitive impairment [62].

It is important to remember that different types of cholesterol are likely to have different effects. While a diet high in low-density lipoprotein (found mainly in saturated animal fats), is implicated in vascular and other diseases, a diet high in high-density lipoprotein (found mainly in fish, olive oil and nuts), may reduce the risk of cognitive impairment, possibly by alleviating the inflammatory response and high blood pressure, as well as improving insulin sensitivity [63,64].

Given the emphasis on weight loss and caloric restriction in recent years, it may seem intuitive that these steps would promote maintenance of a healthy brain. In one study, lower caloric intake was found to be associated with slower age-related cognitive decline and reduced the risk of AD, particularly among individuals with a genetic predisposition for AD [65]. It has been suggested that caloric restriction may reduce cellular oxidative damage and/or lower blood glucose levels [66]. However, there is also some evidence that caloric restriction may increase levels of hormones known as glucocorticoids [66]. Although a temporary increase in these hormones can improve alertness and concentration, long-term exposure is correlated with shrinkage in the hippocampus [67].

Short-term caloric restriction was associated with poorer cognitive performance among obese women [68] and, in a 20-year longitudinal study, significant weight loss increased the risk of cognitive impairment [69]. In a further study, 22 older participants who fasted overnight displayed enhanced memory performance after a dietary intake of protein, carbohydrate or fat, regardless of potential elevation in blood glucose [70]. In general, however, it appears that benefits of moderate caloric restriction for a healthy brain could be substantial, particularly when nutritional deficiencies are avoided [71,66].

Besides major nutrients, micronutrients, particularly vitamins, have gained credence as playing an important role in memory and cognitive performance. Low blood serum levels of vitamins C and E, and β -carotene – all major

antioxidants – may be associated with cognitive decline [72] and AD [73]. Dietary intake or supplementation of a concoction of these vitamins may help to maintain normal cognitive function [74,75]. Results are less clear regarding supplementation with vitamin E only, following some earlier enthusiasm. Some researchers still propose a protective effect of vitamin E against AD [76], while others caution that daily doses higher than 400 international units (IU) of vitamin E may increase the risk of mortality [77]. The possibility that only dietary vitamin E may protect against AD has also been raised [78].

There is some evidence to suggest that light-to-moderate alcohol consumption (up to three alcoholic drinks a day [79], or between one and seven drinks a week [80]) may reduce the risk of cognitive impairment in the elderly compared with those who abstain. Drinking in moderation may contribute to some brain atrophy, but it may also reduce the number of silent infarcts in the brain, a known risk factor for cognitive impairment [81]. In addition, light drinking may reduce blood clotting and blood serum lipid levels, as well as stimulate acetylcholine production in the brain [79].

Medication & supplements

The introduction of ginkgo biloba, a herbal supplement, to the general public was surrounded by enthusiasm due to its presentation as a substance with the potential to temporarily slow cognitive decline in dementia patients in a widely cited study by Le Bars and colleagues [82]. Reduced oxidative stress in the brain and/or increased cerebral blood circulation were the proposed mechanisms of action [83]. However, the evidence that intervention with ginkgo biloba may help maintain cognitive function in nondemented older adults remains inconclusive [83]. For example, a randomized double-blind trial that included 6-week treatment with 180 mg of ginkgo biloba yielded improvements in cognitive performance compared with control [84], whereas the findings of a similarly designed study yielded null results [85].

Estrogen replacement therapy has become a controversial issue during the past few years. While early observational studies found a protective effect against cognitive impairment in women undergoing therapy following the onset of menopause [86], results from a large randomized trial undertaken by the Women's Health Initiative (WHI) Memory Study indicated an increased risk of dementia in women introduced to therapy

with estrogen and progestin after menopause [87]. Drug administration in this study was discontinued approximately 3 years earlier than planned due to an increased risk of heart disease, stroke, pulmonary embolism and breast cancer in the intervention group. It appears that hormone replacement therapy may be an acceptable temporary treatment during menopausal transition, but may not be feasible long-term or when administered after menopause [88].

Inflammation in the brain occurs during the neurodegenerative process that accompanies the progression of AD [89]. Therefore, it might be assumed that therapy with nonsteroidal anti-inflammatory drugs (NSAIDs) may buffer against cognitive impairment. Although observational studies suggest a protective effect related to long-term use of NSAIDs [90], not enough is known to recommend NSAIDs as a preventive strategy for cognitive decline or dementia [91].

Cholinesterase inhibitors have been found to slow the progression of cognitive and behavioral symptoms in patients with AD [92]. Cholinesterase inhibitors prevent breakdown of acetylcholine (a neurotransmitter essential for memory consolidation), thus increasing its overall levels in the brain. Some preliminary evidence suggests that cholinesterase inhibitors may postpone AD onset in individuals with mild cognitive impairment [93], although general guidelines for administration of these drugs to nondemented individuals do not exist, and general use may not be advisable [92]. Similarly, the newer drug memantine (Namenda®), which is thought to reduce glutamatergic excitotoxicity, has been approved for the treatment of moderate-to-severe AD, but has not been adequately tested as a preventive measure in individuals at risk of developing dementia [94].

Stress, personality & mental health

The emotional arousal that accompanies the experience of stress is associated with increased activation of the hypothalamic–pituitary–adrenal (HPA) axis and release of glucocorticoids [95]. Cortisol, a human glucocorticoid, is associated with both stress and depression. While transient increases in cortisol may actually improve cognition, persistently high levels of cortisol may lead to atrophy in the hippocampus [67].

In a meta-analysis of epidemiological studies, Jorm found that depression was associated with a subsequent risk of AD [96]. However, the nature of the association between depression and AD remains questionable, as incipient AD may be a

risk factor for depression [96]. More recently, investigators have started to examine the relationship between personality and AD, with the idea that studying the proneness of an individual to psychological distress is more practical than studying actual distress across their lifetime. Neuroticism, a personality trait that has been associated with both greater reactivity and greater exposure to stress [97], was found to be associated with the risk of dementia approximately 5 years later [98]. However, personality changes are common in people with oncoming dementia. Therefore, the relationship between neuroticism and dementia is also questionable.

While further research is needed, findings linking indicators of lifetime stress and depression to impaired cognition have interesting implications in terms of intervention. These studies raise the possibility that medications or psychotherapeutic interventions for dealing with stress and alleviating depression may have utility for prevention of cognitive decline.

Conclusion

A proportion of our cognitive abilities is determined by unchangeable factors such as genes and early-life environment, making prevention of cognitive deficits and AD impossible for some people. However, other factors do appear to be modifiable and there may be a number of ways to help maintain normal cognition in older adulthood. Some strategies are already available to middle-aged and older individuals to promote cognitive function and delay cognitive difficulties. These strategies include lifestyle modifications as well as specific training of cognitive skills.

Health-related lifestyle factors appear to be important for the prevention of cognitive decline and dementia. Taking part in physical exercise, maintaining optimal levels of blood glucose and blood pressure, treating high cholesterol, and avoiding nutritional deficiencies have been supported as beneficial for preservation of cognitive function. There is also growing empirical evidence that engagement in intellectual, social and physical leisure activities may facilitate maintenance of cognitive abilities. This apparent relationship may be due to intellectual stimulation, stress reduction, or physical health promotion. Randomized clinical trials are required to confirm the association between these types of activities (as well as other epidemiological findings) and cognition. Specific training of cognitive skills has been

found to have positive effects on older adults' cognitive function, although transfer of effects to the performance of real-world activities awaits further investigation.

Again, it must be emphasized that the risk of cognitive decline and dementia may sometimes be difficult to modify given the well-known influence of genetic and early-life factors. In addition, a proper assessment of cognitive problems should include an evaluation of readily identifiable and possibly reversible causes of cognitive impairment, such as medication side effects (for example, anticholinergic drugs and benzodiazepines) and medical conditions such as infection, inflammatory disease or exposure to toxins [99].

Future perspective

Future research should lead to better knowledge of specific, widely applicable strategies to promote the maintenance of cognitive function, as well as better identification of groups who are particularly susceptible to cognitive decline. A related issue is finding the best way to engage individuals in cognition-enhancing strategies. Leisure activities may be one factor that is relatively amenable to population-wide intervention. However, while there is increasing evidence that engaging in leisure activities is beneficial for cognitive function, the specific activities that are most beneficial for avoiding cognitive decline remain to be adequately investigated. Another growing area of research is aimed at answering the question of whether medications used to slow cognitive decline in those with AD may help people who do not have a diagnosable dementia but have a high risk of developing dementia in the future.

A general issue for future research involves examining nonlinear or U-shaped relationships between predictors of interest and memory decline. It is widely believed that the body's biological systems work in conjunction to maintain homeostasis. Thus, if homeostasis is not achieved because of too low or too high levels of nutrients, hormones, or neurotransmitters, or either hypoactive or hyperactive systems, it is possible that this type of deviation from homeostatic range may accelerate aging and cognitive decline. For example, both high and low blood glucose have been associated with impaired cognitive function. Similarly, there is evidence linking high and low blood pressure to the risk of cognitive impairment, while moderate levels may be optimal for avoiding cognitive decline.

This pattern has also been found for alcohol consumption, where having a few drinks per day may be better for maintenance of cognitive function than drinking more or less than that amount. So far, however, the majority of studies of the risk of cognitive decline have focused on

finding linear relationships for exposures of interest.

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Executive summary

Introduction

Engagement in strategies to prevent cognitive decline may reduce the risk of dementia, can improve wellbeing in old age, and can help conserve personal and societal resources.

The concept of cognitive reserve

Various genetic and environmental factors influence cognitive reserve by contributing to brain structure and function and/or improving problem-solving abilities. The concept of cognitive reserve has been used to explain why some older adults experience cognitive impairment while others remain intact.

Some early-life factors, such as socioeconomic status in childhood and education, may influence cognitive decline and the risk of dementia later in life.

Occupation-related activities and engagement in intellectually, socially and physically demanding activities in mid-life or later may reduce the risk of cognitive decline and dementia.

Cognitive training

Cognitive training interventions can improve targeted cognitive abilities in laboratory-based tests. Transfer of the trained skills to everyday activities has not yet been confirmed.

Physical exercise

Relatively strenuous aerobic exercise may provide cognitive benefit to older adults, possibly by promoting vascular health.

Physical health

Chronic health conditions and diseases, such as vascular disease and diabetes, may contribute to cognitive problems.

Optimal ranges of blood pressure and blood glucose are important for maintaining cognitive function in aging individuals.

Diet & nutrition

Deficiencies in some micronutrients, such as folic acid and vitamin B₁₂, may be associated with cognitive decline and impairment. Dietary intake or supplementation of antioxidant vitamins C and E and b-carotene may protect against cognitive decline and impairment. However, high doses of vitamin E may increase the risk of death.

High levels of serum high-density lipoproteins may increase the risk of dementia, while high levels of low-density lipoproteins may reduce the risk.

Moderate caloric intake in the absence of nutritional deficiencies may help maintain normal cognitive function with aging.

Light-to-moderate alcohol consumption may reduce the risk of cognitive impairment in the elderly compared with those who abstain or drink heavily.

Medication & supplements

Some evidence exists that ginkgo biloba may be associated with slowed cognitive decline in AD patients, although findings are still inconclusive. Even less conclusive evidence exists regarding the potential cognitive benefits of ginkgo biloba usage in nondemented individuals.

Estrogen replacement therapy remains a controversial issue. The current evidence suggests that long-term hormone-replacement therapy is not advisable.

Observational studies with long-term users of nonsteroidal anti-inflammatory drugs (NSAIDs) have revealed protective effects. However, more clinical trials are required before recommendations for preventive use of NSAIDs can be made.

Cholinesterase inhibitors may temporarily slow the progression of AD, but more studies are needed before these drugs can be recommended for individuals without dementia.

Mental health

Stress and depression may be associated with damage to the hippocampus and impaired cognition.

Conclusion

Although some factors influencing cognition and risk of dementia cannot be amended, there are multiple strategies that may postpone cognitive decline and impairment.

Future research should aim to identify groups of individuals at the highest risk for cognitive problems, find optimal ranges for protective factors, and implement strategies that may best facilitate cognitive performance.

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