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# Strategies for Preventing Cognitive Decline in Healthy Older Adults

## Stratégies de prévention du déclin cognitif chez les adultes âgés en santé

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**Abstract**

**Objective:** Many advances have been made in the understanding of age-related changes in cognition. As research details the cognitive and neurobiological changes that occur in aging, there is increased interest in developing and understanding methods to prevent, slow, or reverse the cognitive decline that may occur in normal healthy older adults. The Institute of Medicine has recently recognized cognitive aging as having important financial and public health implications for society with the increasing older adult population worldwide. Cognitive aging is not dementia and does not result in the loss of neurons but rather changes in neurotransmission that affect brain functioning. The fact that neurons are structurally intact but may be functionally affected by increased age implies that there is potential for remediation.

**Method and Results:** This review article presents recent work using medication-based strategies for slowing cognitive changes in aging. The primary method presented is a hormonal approach for affecting cognition in older women. In addition, a summary of the work examining modifiable lifestyle factors that have shown promise in benefiting cognition in both older men and women is described.

**Conclusions:** Much work remains to be done so that evidence-based recommendations can be made for slowing cognitive decline in healthy older adults. The success of some of these methods thus far indicates that the brains of healthy older adults are plastic enough to be able to respond to these cognitive decline prevention strategies, and further work is needed to define the most beneficial methods.

**Abrégé**

**Objectifs :** De nombreux progrès ont été réalisés dans la compréhension des changements de la cognition liés à l'âge. À mesure que la recherche explique les changements cognitifs et neurobiologiques qui surviennent avec le vieillissement, il y a un intérêt accru pour élaborer et comprendre des méthodes afin de prévenir, ralentir ou renverser le déclin cognitif qui peut survenir chez des adultes âgés en santé. L'Institute of Medicine a récemment reconnu que le vieillissement cognitif a d'importantes implications financières et de santé publique pour la société, étant donné le vieillissement mondial de la population. Le vieillissement cognitif n'est pas la démence et ne produit pas la perte de neurones, mais plutôt des changements de neurotransmission qui affectent le fonctionnement du cerveau. Le fait que les neurones sont structurellement intacts mais que leur fonctionnement peut être touché par le grand âge implique qu'il y a un potentiel d'y remédier.

**Méthodes et résultats :** Cette revue présente des travaux récents qui utilisent des stratégies basées sur les médicaments pour ralentir les changements cognitifs de la vieillesse. La principale méthode présentée est une approche hormonale pour influer sur la cognition chez les femmes âgées. En outre, un résumé des travaux examinant des facteurs de mode de vie modifiables qui sont prometteurs pour la cognition chez les femmes et les hommes âgés est décrit.

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**Conclusion :** Il reste beaucoup à faire avant de pouvoir publier des recommandations fondées sur des données probantes en vue de ralentir le déclin cognitif chez les adultes âgés en santé. Le succès de certaines de ces méthodes jusqu'ici indique que le cerveau des adultes âgés en santé est assez malléable pour être en mesure de répondre à ces stratégies de prévention du déclin cognitif. Il faut plus de recherche pour définir les méthodes les plus bénéfiques.

**Keywords**
cognitive aging, cognitive decline, estrogen, exercise, cognitive training, diet

In the next 40 years, the United States will experience a dramatic increase in adults living to old age, and older adults will outnumber children younger than 14 years for the first time by 2050. In Canada, by 2030, close to 1 in 4 persons will be aged 65 years or older, compared with 15.3% in 2013. While a number of scientific advances have contributed to the increased life expectancy, methods for slowing processes responsible for cognitive decline remain to be determined. Decline of cognitive functioning has become of increasing concern because of potential degradation of the quality of life as well as the threat to independence feared by many older adults.[1] With increased age, adults may experience declines in cognition that fall short of dementia but still affect functional abilities and independence.[1] The goal of successful aging is to maintain intact cognitive functioning all the way until death. Normal cognitive aging is not dementia and does not result in the loss of neurons[2]; rather, there are changes in brain functioning.[1] The preservation of structural aspects of the brain in normal aging implies that there is the possibility of preventing, slowing, or reversing cognitive changes. This review will examine the potential medication-based as well as lifestyle-based factors that may be useful for influencing cognitive decline that occurs in healthy older adults. Understanding methods for slowing cognitive decline will have a positive impact on older adults themselves as well as the societies in which they live as the aging population continues to grow worldwide.

Much research has focused on the processes involved in the development of cognitive impairment that leads to dementia. Efforts are moving from focusing on the treatment of already identified demented patients to developing strategies that will accurately identify patients with predementia conditions or risk factors for dementia and design effective treatments to alleviate symptoms and prevent or slow progression to a demented status. Mild cognitive impairment (MCI) describes a transitional state between normal cognitive aging and mild dementia,[3,4] and much research focuses on preventing the conversion to dementia. However, once a dementia process has begun, in the case of MCI, it may be too late to reverse the damage to neural systems. Thus, studies have examined healthy adults at younger ages before dementia processes have started. Studies examining genetic risk factors such as apolipoprotein E (APOE)[5] as well as beta-amyloid load[6] in the brain are beginning to delineate who is at risk for pathological decline with increased age. In addition, much work has focused on ways to prevent cognitive decline, from strategies ranging from medications to exercise. This review will examine medication-based methods and hormones in particular for potentially affecting cognitive decline. The risk of dementia is greater in women,[7] and women with dementia experience poorer outcomes compared with men,[8] thus implying a role for gonadal steroids in the development and treatment of cognitive changes in aging. This review will also briefly examine lifestyle modifications that influence cognition in aging that are likely to have benefits for both men and women but do require behavioral modifications, which come with their own difficulties with regard to adherence. First, I will briefly describe what is meant by cognitive aging and the current state of the literature.

## Cognitive Aging

The field of cognitive psychology seeks to discover the form of mental representations and the processes that access them. It is the study of how people perceive, learn, remember, and think about information. Cognitive aging examines what happens to these processes during aging. It examines how cognition changes over time within and between people. Prior research shows that older adults perform more poorly than younger adults on cognitive tasks, specifically tests of attention, working memory, and episodic memory.[9,10] Older adults tend to perform better than younger adults on tasks on which they can use the wisdom they have experienced during their lives, such as some tests of judgment and problem solving.[11] With the widespread use of functional neuroimaging, questions have been addressed regarding the underlying structural and functional changes in the brain that affect cognition during aging. Studies have shown that atrophy in the medial temporal and hippocampal regions are often seen in adults with dementia.[12] Changes in functional brain activation patterns between older and younger adults are frequently seen but appear to depend on the task type, the subjects' performance, and the amount of dementia progression.[13,14] More recent studies using positron emission tomography and ligands that adhere to beta-amyloid and allow its visualization have been used to examine the amyloid load in the brain of healthy adults at younger ages. A meta-analysis found that beta-amyloid appears approximately 20 years before any clinical signs of dementia are present, and approximately 20% of people without dementia show significant beta-amyloid accumulation in the brain.[15] Thus, there is currently a discrepancy between the onset of the neurobiological processes that are found in adults experiencing

cognitive decline and the ability to detect these declines on clinical and laboratory-based cognitive testing measures. However, identifying those at risk at a younger age will benefit people as more methods to slow cognitive changes are being discovered.

A parallel literature to the cognitive psychology of aging exists in cognitive geriatric psychopharmacology examining the effects of medications on age-related changes in cognition. Research in this field has focused on examining age changes in neurotransmitter systems and the effects of agonists[16] and antagonists[17] on cognitive task performance. These studies have been successful in identifying chemical systems associated with age- and disease-related cognitive deterioration and in developing therapies for those with dementia. However, little work has been done to examine neurotransmitter modulatory medications in normal aging.

Additional studies have focused on hormonal influences on cognition and cognitive decline. There are gender differences in the prevalence of Alzheimer's disease (AD), which leads to the hypothesis that there is a role for gonadal steroids in influencing the risk and resilience for cognitive decline and dementia in older age. While the evidence supporting hormonal use for prevention of cognitive decline is controversial, the preclinical evidence and underlying biological mechanisms suggest that the hormone story should continue to be investigated. The evidence supporting and refuting the proposal that hormones have the potential to be beneficial for cognition in aging is described below.

## Aging and Cognitive Decline in Women

Women appear to be at higher risk for AD, even after controlling for increased life span in women, particularly if they carry the APOE4 allele.[7] In addition, women with AD show greater cognitive decline than men with AD.[8] Given these gender differences, many studies have examined the role of gonadal steroids in the risk and development of dementia. There is considerable epidemiologic evidence from both prospective and case-control studies that estrogen use in postmenopausal women may decrease the risk of the development and/or expression of AD (e.g., ref. 18). The gonadal steroid estradiol (E2) may slow or prevent cognitive decline, enhance cognitive functioning, and lower the risk of developing AD.[19-22] However, large controlled trials of estrogen alone as a therapy for mild to moderate AD have been equivocal, showing no significant effect on cognitive measures of long-term progression.[23] Thus, it seems that once a dementia process has begun, hormonal treatment with estrogen is not effective. However, given the gender differences in dementia risk and the ability of gonadal steroids to influence cognition, further consideration of the effects of hormones on cognition in aging is warranted. In addition, the hormone change at menopause has many biochemical effects on a woman's body, including the brain. Moving the focus to the menopause transition rather than an older age at which dementia is diagnosed allows an examination of the development of the processes that may be involved in dementia.

Menopause occurs around age 51 years in women and is arguably the most important biochemical event in a woman's adult life. This major hormonal change is likely to affect brain functioning and cognition as the brain is a major target for circulating estrogens and the change in estrogen levels after menopause has implications for cognitive functioning. Clinical and preclinical studies have linked estrogen and cognition,[24,25] and it has been hypothesized that menopause has detrimental effects on cognition that are over and above the expected effects of normal aging. Studies have shown that women report subjective changes in cognitive functioning around the menopause transition,[26] and 1 study found that up to 60% of women reported subjective changes in cognition after menopause.[27] Studies have suggested that impairments or decreases from premenopausal levels of cognitive functioning occur in specific domains, including memory, attention, problem solving, and motor skills (e.g., ref. 28). The most consistent evidence for a direct effect of estrogen on cognition is from studies of surgically menopausal women. Sherwin[29] studied women after total abdominal hysterectomy with random assignment to estrogen or placebo for 3 months and found that the treated group showed preservation of verbal memory while the placebo group showed a significant decline.

However, the presence of objective changes in cognition after menopause in naturally menopausal women is equivocal. Some studies have suggested that decreases from premenopausal levels of cognitive functioning occur in specific domains including memory, attention, problem solving, and motor skills.[28,30,31] Other studies have not found objective changes in cognition after menopause.[32-34] Studies published as part of the Women's Health Initiative study (WHI) have examined the impact of a combined conjugated estrogen (CEE) plus progestin and CEE alone treatment on the development of dementia. The WHI Memory Study, following up a part of this cohort, showed that the relative risk of diagnosis of dementia in the active treatment group was approximately twice that of the placebo group.[35]

There are a number of caveats regarding these data that need to be taken into account.[36] Most importantly, the average age of the women in the WHI study at treatment onset was 63.3 years, with two-thirds between the ages of 60 and 70 years, far past menopause. Brinton and others have proposed the so-called "healthy cell bias of estrogen benefit,"[37,38] suggesting that hormone therapy may benefit healthy neurons but neurologically deficient neuronal systems may be compromised by long-term treatment. The human extension of this has been defined as the "critical period hypothesis,"[39-42] suggesting that estrogen has maximal protective benefits on cognition in women when it is initiated closely in time to the menopause. Shao et al.[43] recently demonstrated that hormone use around menopause predicted decreased rates of dementia in later life compared with never users. This finding highlights the importance of the hormone change at menopause on

cognition in later life and the use of estrogens close to the beginning of menopause on protection from dementia.

Experimental evidence for a critical period for beneficial effects of estradiol on cognition in postmenopausal women was shown by Dumas and colleagues.[44] Our model used a cholinergic challenge procedure that was expected to impair cognition in healthy postmenopausal women. This study found that 3 months of E2 compared with placebo attenuated the impairment seen during anticholinergic medications on verbal memory measures in younger postmenopausal women (mean age 55 years) only. In older postmenopausal women (mean age 74 years), E2 increased the anticholinergic impairment.[44] Thus, the results of this study emphasized the importance of cholinergic integrity in observing a beneficial effect of estrogen, which may be observed more readily in younger postmenopausal women. This finding further specifies the healthy cell hypothesis to include cholinergic system integrity and provides evidence for one potential mechanistic pathway by which estrogen may have beneficial effects on cognition in younger postmenopausal women with normally functioning cholinergic systems.

Although it has been more than 10 years since the WHI study was stopped because of increased risks of estrogen and progesterone, the data have continued to be examined, and further recommendations have been proposed with regard to the use of these hormones in postmenopausal women. Generally, the recommendations are that estrogen is safe and effective for younger women around the time of menopause for menopausal symptom relief.[45] There has been no evidence that estrogen should be used for the prevention of dementia. Given the risks of estrogen for some women and for older women in particular, we examined the effects of tamoxifen on cognition in postmenopausal women in our cholinergic model.[46] Tamoxifen (TMX) is a nonsteroidal oral selective estrogen receptor modulator used as adjuvant therapy in both women and men with breast cancer and as palliative therapy in prostate cancer. TMX has estrogen-like activity in some tissues and anti-estrogen effects in others. In our cholinergic challenge model, TMX partially blunted or reversed the cognitive-impairing effects of cholinergic receptor antagonists on measures of verbal memory and spatial navigation. Intriguingly, APOE4+ women (who are at a higher risk of developing AD) showed a greater benefit of TMX in reversing the anticholinergic-induced cognitive impairment. These data suggest that TMX has effects that are beneficial to episodic memory processes that may be hippocampally mediated because both verbal memory and spatial navigation have been shown to be hippocampal tasks. Provocatively, APOE genotype appears to be important in modulating the effect of TMX on cholinergic systems in women after menopause. Further studies are needed to examine longer-term use of TMX in normal healthy women to examine the possibility of continued benefits to cognition and to evaluate the risks.

In sum, prospective and some longitudinal studies indicate beneficial effects of at least early estrogen therapy on cognitive functioning of postmenopausal women. However, the randomized controlled trials show different results depending the age of the women, the type of estrogen, and the inclusion of progesterone. While the epidemiological and preclinical data continue to show positive population-level effects and neurobiological mechanisms, a role for the use of estrogen on affecting cognition in later life should continue to be examined.

## Lifestyle Factors to Modify Cognitive Aging

Thus far, evidence has been reviewed that examined hormonal effects on brain functioning in older women and has not described any methods for potentially affecting cognitive decline in men. Recently, a number of lifestyle factors have been examined that may have the potential to improve cognition and result in more efficient brain functioning in both women and men. Modifiable lifestyle factors that have been examined with potential benefits on cognition in aging include exercise, cognitive training, diet, yoga, tai chi, mindfulness, and social engagement. Results show a number of different patterns from benefits to null effects in older adults. A complete review of each of these is beyond the scope of this review, but some summary findings are presented below in the areas of exercise, cognitive training, and diet.

Most notable are the studies showing that exercise in older adults improves cognition as well as brain functioning (i.e. refs. 47, 48). Specifics regarding whether aerobic exercise versus strength training[49] has the most beneficial effects on cognition are still being determined. These studies have shown improvements in performance measures as well as brain structural measures.[48] These findings indicate the brain remains plastic enough to experience the benefits of exercise, and it allows optimism for continued examination of exercise as a way to prevent, slow, or reverse cognitive decline in aging.

In addition, some benefits of cognitive training on cognition in healthy older adults have been seen.[50,51] However, other studies have not found benefits of video games in older adults.[52] The effects of cognitive training are somewhat more difficult to tie down since the issue of transfer effects appears to be very relevant in this context. Studies have shown that training can improve performance on the particular task that is being trained. However, the transfer to a different cognitive domain or even a within-domain task is not always observed.[53] Further studies are needed to determine what factors lead to transferable improvements in cognition in older adults. This is information that may have an immediate financial impact on some individual as there is much marketing of these computerized training products that are being sold to influence cognition.

One final lifestyle modification that may influence cognition in older adults is diet. Dietary interventions and their effects on cognition and brain functioning are less well-studied in humans in terms of randomized controlled studies, although observational studies show potential benefits for the Mediterranean-style diet to lessen the cognitive decline with aging.[54-58] One interventional trial comparing a low-fat diet with supplements of either olive oil or mixed nuts also revealed benefit of the Mediterranean-style diet on cognition.[59] In a

recent systematic review and meta-analysis, Lehert and colleagues[60] examined the 12 potentially modifiable risk factors for cognitive decline in aging. They found that the greatest although small benefits were observed with a Mediterranean diet plus tai chi on global cognition and a Mediterranean diet plus olive oil and soy on memory. Overall, more randomized trials are necessary to make evidence-based recommendations about diet to influence cognitive decline in aging. Specifically, studies are needed to delineate specific nutrients that are beneficial to cognition so that recommendations can be made that have the potential to protect the brain from cognitive decline in older as well as younger adults.

## Conclusions

Cognitive aging is not a disease or disorder but rather the normal developmental process that occurs during adulthood. With the increasing older adult population, the financial impact on society will continue to grow. Methods to prevent, slow, or reverse cognitive decline with aging should continue to be examined. Medication-based strategies such as hormone use have been examined in a number of studies, and the results appear mixed. The epidemiological and preclinical data continue to suggest benefit of estrogens on cognition. However, randomized studies continue to produce mixed results. Thus, further studies are needed.

In addition, recent work has examined the influence of modifiable lifestyle factors on cognitive change in older adults. These studies appear to have mixed results, but the fact that there are some benefits to exercise, cognitive training, and diet implies that the brains of healthy older adults remain plastic enough to observe the benefits of these approaches. Detailing the specific recommendations that are the most useful for brain functioning in older age will continue to take much research. Thus far, the evidence, while mixed, appears optimistic for the development of evidence-based strategies that will prevent, slow, or reverse cognitive decline in health older adults.

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