

# Cognitive Decline in Aging Women and What They Can Do About It

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The intense interest in the etiology and prevention of degenerative diseases that are common in older age can be attributed to a variety of factors. First, there has been a dramatic increase in life expectancy in industrialized countries during the past century due, in part, to the decrease in maternal and childhood mortality, the availability of vaccines to control many infectious diseases, the development of antibiotics and other drugs to treat chronic illnesses, and improvements in the standard of living. Of course, the consequences of these medical and social advances mean that, on average, people in industrialized countries are living well into their eighth decade of life. Unfortunately, however, this increase in life expectancy has not been paralleled by a decrease in the rate of disability before death.

The result is that more people are living longer with a disability toward the end of life, which causes considerable suffering for individuals and their families, and a heavy financial and social burden for society.<sup>1</sup> Prominent among the degenerative diseases of older age are those that affect cognitive functioning. This ar-

ticle will address whether all aspects of cognition inevitably decline with increasing age, and explore possible vulnerability factors with regard to cognitive decline. Questions concerning the efficacy of preventive strategies against cognitive aging and the potential modifiability of cognitive decline will also be discussed.

## Normal Cognitive Aging

There is now a considerable amount of evidence to suggest that changes in cognition occur with normal aging. Although longitudinal studies have generally failed to identify age-related cognitive decline before the age of 60 years,<sup>2</sup> cross-sectional studies of cognitively healthy people have found linear declines in cognition across the lifespan.<sup>3</sup> Therefore, there seems to be general agreement that declines in cognitive function occur after the age of 60 and affect more than 40% of individuals older than 60 years of age.<sup>4</sup> From a clinical perspective, the fact that nondementia memory decline can interfere with an older person's daily functioning renders it a meaningful clinical issue.<sup>5</sup>

It has also become clear that age-related cognitive changes are selective rather than diffuse. Across cognitive domains, memory performance, in particular, undergoes decline with increasing age.<sup>6,7</sup> A 1999 study by Small et al<sup>7</sup> found no apparent changes in tests of language, visuospatial ability and abstract reasoning, but memory for the acquisition and early retrieval



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of new information becomes somewhat compromised with increasing age. Working memory, the ability to hold information in memory while it is being manipulated, also declines with increasing age.<sup>8</sup> Since the acquisition and retrieval of new information is mediated by the hippocampus, and because working memory is primarily a function of the prefrontal cortex, interest in cognitive aging has largely focused on these two brain regions.

Neuroanatomical evidence and findings from imaging studies suggest that the integrity of some brain areas is more vulnerable than others to aging processes. Changes tend to occur most profoundly in the prefrontal cortex, in the hippocampus and in the parietal regions of the brain. These same anatomical locations subserve the specific cognitive functions that decline with normal aging, including verbal memory and working memory. The underlying pathologic basis of cognitive decline is inevitably related to the loss of synapses, neurons, neurotransmitters and neural networks.<sup>9</sup> For example, in medically and cognitively healthy older adults, longitudinal magnetic resonance imaging (MRI) scans showed that the annual rate of brain tissue loss was  $5.4 \pm 0.3 \text{ cm}^3$  per year, with the frontal and parietal lobar regions showing the greatest decline.<sup>10</sup> When structural-functional relationships were explored using MRI and neurologic testing in older healthy adults and in those with Alzheimer's disease, the volume of the hippocampal formation predicted performance on most learning and memory measures across the spectrum of normal aging and

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Alzheimer's disease.<sup>11</sup> However, neuronal loss may not be an inevitable feature of normal brain aging. Indeed, there is evidence that neurogenesis (the synthesis of new neurons) continues throughout life, including old age.<sup>12</sup>

### Factors that can Negatively Influence Cognitive Aging

Although the influence of aging on cognitive function is complex and likely involves an interaction of several factors, there is evidence to implicate several specific biological and environmental factors as modulators of cognitive aging (Table 1).

*Apolipoprotein E (APOE).* The APOE locus on chromosome 19 is associated with both familial and sporadic Alzheimer's disease, and is expressed with relative selectivity in hippocampal neurons.<sup>13</sup> APOE<sub>4</sub> has often been associated with greater risk of cognitive decline with aging.<sup>14</sup> Currently, this genetic factor is not modifiable.

*Homocysteine.* Since the level of homocysteine increases with age and is recognized as a risk factor for cardiovascular and cerebrovas-

cular disease, several cross-sectional studies sought to determine whether there is a relationship between homocysteine levels and cognitive aging. Most have found a modest inverse relationship between homocysteine levels and cognitive function in cognitively healthy older individuals, a relationship that was judged by researchers as unlikely to be biologically important.<sup>15,16</sup>

*Hypercholesterolemia.* The evidence regarding whether or not hypercholesterolemia is a risk factor for cognitive decline in older individuals is inconsistent. In a longitudinal study undertaken in Finland,<sup>17</sup> midlife elevated serum cholesterol levels ( $>6.5 \text{ mmol/L}$ ) were a significant risk factor for mild cognitive impairment (OR, 1.9; 95% CI, 1.2-3.0). On the other hand, in the longitudinal Framingham Heart Study,<sup>18</sup> lower naturally occurring levels of total cholesterol were associated with poorer performance on several cognitive measures, including verbal fluency, concentration, and executive functioning (implicated in complex cognition, such as novel problem-solving, and in implementing schemas that organize behavior across time). The findings on the role of hypercholesterolemia in the risk for Alzheimer's disease also fail to provide evidence that hypercholesterolemia is a risk factor. In a longitudinal Australian study,<sup>19</sup> hypercholesterolemia was actually associated with a protective effect against the development of dementia and cognitive decline, and in a US study of 2,000 people over the age of 65<sup>20</sup> there was no association between total serum cholesterol or high-density lipoprotein (HDL) cholesterol in late life and

subsequent risk of Alzheimer's disease. Finally, although use of statin drugs was associated with a slight reduction in cognitive decline in an elderly population, the relationship could not be completely explained by the serum cholesterol-lowering effect of the statins.<sup>21</sup> Currently, therefore, the weight of the evidence fails to support the hypothesis that hypercholesterolemia is an important risk factor for cognitive decline with aging.

**Metabolic syndrome.** In a 5-year, prospective, observational study of 74-year-old men and women who were cognitively healthy at the time of their initial recruitment, those with metabolic syndrome (defined as having at least three of the following factors: abdominal obesity, hypertriglyceridemia, low HDL levels, hypertension and hyperglycemia) and high levels of inflammation (interleukin-6 and C-reactive protein) had a significantly increased risk of cognitive impairment.<sup>22</sup>

**Type 2 diabetes mellitus (DM).** A review of prospective and cross-sectional studies concluded that there was a positive association between type 2 DM and cognitive impairment, particularly for memory and executive functions.<sup>23</sup> In the Nurses' Health Study,<sup>24</sup> 74-year-old women with type 2 DM had marginally worse baseline performance and greater cognitive decline over a 2-year period than did women without DM, as assessed by cognitive tests administered via telephone. Although women using insulin had significantly lower cognitive scores than those without DM, the cognitive scores of women with DM who were using oral hypoglycemic medications were not

different from those of women without DM.

**Hypertension.** A study following 500 elderly individuals for 6 years found that those with higher blood pressure (BP) had greater deterioration on measures of mental status, processing speed, memory and visuospatial ability.<sup>25</sup> Although there is not unanimous agreement among studies, the weight of the evidence suggests that elevated BP is a predictor of cognitive decline.

**Depression.** Numerous longitudinal<sup>26</sup> and cross-sectional studies<sup>27</sup> have documented a positive relationship between depression and cognitive decline in older people. Severity of depression predicted greater cognitive decline in older women 4 years following their diagnosis of depression.<sup>28</sup> A recent meta-analysis of this literature confirmed

that there was a significantly increased relative risk of cognitive impairment in depressed older people in both prospective (RR = 1.87; 95% CI, 1.09-3.20) and case-control studies (RR = 2.01; 95% CI 1.16-3.50).<sup>29</sup> However, the underlying mechanisms and the nature of this association are still unclear. Among the possible explanations are that depression is a prodrome of cognitive decline, that depressive symptoms are a reaction to subjectively perceived cognitive decline, or that the pathophysiologic mechanisms for depression and cognitive decline overlap. The fact that high levels of cortisol are sometimes associated with depression and can also cause neuronal death and cognitive decline<sup>30</sup> could also explain the co-occurrence of these two clinical syndromes.

### Table 1. Biological and Environmental Factors Implicated as Modulators of Cognitive Aging

- **Apolipoprotein E<sub>4</sub> (APOE<sub>4</sub>):** APOE<sub>4</sub> has been associated with a greater risk of cognitive decline in aging. This genetic factor is not modifiable.<sup>13,14</sup>
- **Homocysteine:** There may be a modest inverse relationship between homocysteine levels and cognitive function in cognitively healthy older individuals, but researchers conclude it is unlikely to be biologically important.<sup>15,16</sup>
- **Hypercholesterolemia:** The evidence linking hypercholesterolemia and cognitive decline in older individuals is inconsistent, and the data do not yet support this hypothesis.<sup>17-21</sup>
- **Metabolic syndrome:**\* Metabolic syndrome and high levels of inflammation were linked to a significantly increased risk of cognitive impairment in one study.<sup>22</sup>
- **Type 2 diabetes mellitus:** Studies have concluded that there is a positive association between type 2 diabetes mellitus and cognitive impairment, particularly for memory and executive functions.<sup>23,24</sup>
- **Hypertension:** The weight of the evidence suggests that elevated blood pressure is a predictor of cognitive decline.<sup>25</sup>
- **Depression:** A positive relationship between depression and cognitive decline in older individuals has been documented.<sup>26-30</sup>

\*Metabolic syndrome raises the risk of type 2 diabetes mellitus, heart attack, stroke and premature death, and is defined by having at least three of the following risk factors at the same time: abdominal obesity, hypertriglyceridemia, low high-density lipoprotein cholesterol, hyperglycemia and high blood pressure.

### Can Anything Protect Against Cognitive Aging?

Because genetic vulnerability is not modifiable, the question arises as to whether there are strategies that might be implemented at midlife or afterwards that could protect against cognitive decline in later life. In fact, there is now considerable information that a variety of strategies could help to preserve cognitive function during the latter part of the lifespan (Table 2).

**Education.** Numerous studies have found that years of formal education have a protective effect on cognitive aging. For example, having more than 8 years of education was associated with maintenance of cognitive function during aging in a longitudinal study of nearly 1,500 individuals.<sup>31</sup> Likewise, in the MacArthur Studies of Successful Aging,<sup>32</sup> low levels of education was the strongest predictor of cognitive decline in tests of verbal and nonverbal memory, and conceptualization and nonverbal abilities over 2.5 years in a sample of generally healthy 70- to 79-year-olds, a finding that was recently replicated.<sup>33</sup> Moreover, the influence of educational level on cognitive aging appears to be somewhat independent of socioeconomic status.<sup>34</sup> Therefore, more years of formal education seems to modulate the age-related decrement often seen in long-term verbal memory.

**Estrogen therapy (ET).** Presently, there is a considerable body of literature on the putative protective effect of ET on aspects of cognitive functioning in women. While a comprehensive account of the findings will not be undertaken here, an attempt will be made to summarize and interpret this body

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of knowledge. Whereas randomized controlled trials of surgically menopausal women and some studies of naturally menopausal women have shown that ET helps to maintain aspects of cognition—particularly verbal memory—not all studies have confirmed those findings.<sup>35</sup> While methodologic differences between studies—including their experimental designs, neuropsychological tests used (or not used), and the diversity of the populations studied—could account for some of the inconsistencies between studies, disagreement about the cognitive effects of ET nevertheless remains. The findings from the Women's Health Initiative Memory Study (WHIMS),<sup>36</sup> in which ET failed to protect against cognitive decline in women who were, on average, 70 years old when they started treatment, further complicated the issue. The so-called critical period hypothesis was recently formulated in the attempt to resolve the inconsistencies in the estrogen and cognition literature.<sup>37</sup> It holds that ET optimally protects against cognitive decline

when it is administered to women close in time to menopause, whereas initiation of treatment more than 10 years following menopause is not beneficial and may even cause harm. Indeed, a growing body of evidence from basic neuroscience, and from rodent, non-human primate, and human studies supports the idea that the administration of ET to 45- to 55-year-old women protects aspects of cognitive functioning but is largely without effect when treatment is initiated in postmenopausal women over the age of 60 years.<sup>38,39</sup> There is also reason to believe that the initiation of ET in women at the time of the menopausal transition for a period of 2 to 3 years may confer enduring benefit on cognitive functioning 15 years later.<sup>40</sup> Although it is unlikely that a 30-year randomized trial will ever be carried out to prospectively test the critical period hypothesis, the variety and wealth of the currently available supportive evidence is compelling.

**Alcohol consumption.** In the Nurses' Health Study<sup>41</sup> two telephone assessments of cognitive function were carried out over a 2-year interval in approximately 12,000 women whose mean age was 74 years. Moderate drinkers (consumption of less than 15 g of alcohol per day [about one drink]) had better mean cognitive scores and a significantly lower relative risk of cognitive impairment and cognitive decline than nondrinkers. Although the adverse effects associated with excessive alcohol consumption suggest caution in recommending alcohol intake, these findings nevertheless suggest that moderate alcohol consumption in older women may be

protective with regard to cognitive aging.

*Physical activity.* Accumulating evidence from studies of older women suggests that physical activity may reduce the risk of early cognitive decline. In a recent randomized controlled trial,<sup>42</sup> 66-year-old women and men who were assigned to a 6-month aerobic cardiovascular fitness training program performed better on a test of executive function in association with an increase in frontal and parietal activity as measured by functional MRI compared with a control group (stretching and toning exercises only). These findings suggest that even moderate aerobic activity may protect against cognitive aging in individuals over the age of 65 years.

*Leisure activities.* While the “use it or lose it” adage has frequently been applied to cognitive aging, until fairly recently there have been few empirical studies to support it. In a longitudinal study of older adults, there was a significant

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positive relationship between cognitively complex leisure-time activities (the number of books and magazines read, and numbers of hobbies) and better cognitive function in both women and men.<sup>43</sup> In the longitudinal Bronx Aging Study,<sup>44</sup> higher levels of cognitive activity participation (reading, writing, crossword puzzles, board or card games and group discussions)

were associated with a lower risk of developing amnesic (specifically involving deficits in memory) mild cognitive impairment in individuals whose average age was 79 years. In another recent longitudinal study of 64-year-old women and men in China,<sup>45</sup> more leisure time spent reading and playing board games was associated with a significantly reduced risk of cognitive impairment, whereas more time spent watching television was associated with an increased risk of cognitive impairment in this cohort.

### Conclusions

Although a significant proportion of the population will experience cognitive decline with increasing age, its occurrence is modified by several factors. Carriers of the APOE allele are at higher risk of both cognitive decline with aging and of Alzheimer’s disease, and this genetic factor is not modifiable. No studies have directly tested whether strategies such as participation in cognitively challenging leisure activities, etc., as previously discussed, might delay the onset of cognitive decline in APOE carriers. While such an investigation would be highly worthwhile, it would be difficult to implement.

The ubiquitous finding that education has a protective effect on cognitive aging has stimulated interest in the possible causes for this relationship. Prominent among the proposed explanatory theories is the concept of “cognitive reserve.” This hypothesis proposes that enhanced neuronal structure and brain function engendered by exposure to complex, stimulating and challenging educational experiences may

### Table 2. What Can Protect Against Cognitive Aging?

- *Education level:* Studies have shown a significant positive correlation between higher education level and greater protection against cognitive decline in aging.<sup>31-34</sup>
- *Estrogen therapy (ET):* Studies have found a possible protective effect, particularly on verbal memory, when ET was initiated at the time of or shortly following menopause; however, not all studies have confirmed this finding, and disagreement remains about timing of ET as well as its effectiveness.<sup>35-40</sup>
- *Moderate alcohol consumption:* Moderate drinkers (less than 15 g alcohol/day—approximately 1 drink) had better cognitive function and a lower risk of impairment and decline than did nondrinkers in the Nurses’ Health Study.<sup>41</sup>
- *Physical activity:* Physical activity may reduce the risk of early cognitive decline; even moderate aerobic activity may protect against cognitive aging in individuals over age 65.<sup>42</sup>
- *Participation in leisure activities:* Involvement in cognitively complex leisure-time activities—especially reading, crossword puzzles and board games—is associated with a lower risk of developing mild cognitive impairment.<sup>43-45</sup>

protect against neuronal degeneration.<sup>46</sup> An additional possibility is that enriched neuronal networks may delay cognitive decline even in the presence of structural and functional deterioration in the aging brain. If this were true, then elderly people with more years of education would be less likely to manifest clinical signs of cognitive aging compared with elderly of the same age with fewer years of formal education. Indeed, findings from quantitative MRI studies that compared brain structure among elderly individuals with different levels of education support the cognitive-reserve hypothesis. For example, there was a significant positive relationship between white matter lesions, cerebral atrophy, and low levels of education in nondemented older adults living in the community.<sup>47</sup> Moreover, among cognitively intact elderly, each year of education was associated with an increase in sulcal cerebrospinal fluid (an indirect marker of cerebral atrophy) although there was no relationship between years of education and age-related volume loss of the cerebral hemispheres.<sup>48</sup> One interpretation of these findings is that more years of education can delay cognitive decline even in the presence of increasing cerebral atrophy, consistent with the reserve hypothesis. In a review of studies of cognitively healthy elderly,<sup>49</sup> investigators used psychometric instruments to assess cognitive status, and found that memory ranked high among the cognitive functions that were protected by education. Of course, there is also a plethora of evidence to show that lower levels of education are associated with a greater risk of Alzheimer's disease.<sup>50</sup>

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Since neurogenesis appears to continue throughout life into old age,<sup>12</sup> the cognitive-reserve hypothesis could also explain the apparent protective effect of cognitively challenging leisure activities and physical training on cognitive function in older age. Since the brain retains plasticity in older age, stimulating the brain through participation in such activities should be encouraged in people of all ages, but especially, perhaps, in those over the age of 60.

Finally, two other conclusions may be drawn from this brief overview of cognitive decline with aging. The first is the general observation that individuals who are more physically fit and who have fewer chronic illnesses are at lower risk for cognitive decline as they grow older. Second, despite the research findings on the benefits of higher education, cognitively challenging occupations and leisure activities,

and ET in younger menopausal women, it is important to acknowledge that their efficacy most likely lies in their ability to delay cognitive decline and the clinical manifestations of Alzheimer's disease. That is, there is currently no reason to believe that these cognitive-enhancing and biological strategies would have any effect on the actual etiologic factors that underlie cognitive decline and Alzheimer's disease, which are currently unknown. On the other hand, in view of the continuing increase in life expectancy, the implementation of strategies that could delay cognitive decline could result in enormous personal and societal benefits with regard to maintaining the quality of life for our elderly populations.

Because of a general heightened awareness of the need to institute prophylactic, lifestyle measures to protect their health as they age, many middle-aged women now seek information from their health-care providers regarding measures they can take to prevent cognitive decline in the future. Possible protective factors against cognitive decline that have emerged from this review include the initiation of ET at the time of menopause for 2 or 3 years, moderate alcohol consumption, aerobic physical activity, and involvement in cognitively complex leisure-time activities such as reading, doing crossword puzzles and playing board games. Of course, reducing risk factors for physical diseases such as metabolic syndrome, type 2 diabetes mellitus, and hypertension would also protect against cognitive decline with aging. Finally, the evidence that depression

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is positively associated with cognitive decline in women suggests that it is more important than ever to diagnose and treat depression in postmenopausal women, not only to alleviate the suffering caused by untreated depression, but also to eliminate it as a possible risk factor for cognitive decline. ■

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*This article includes discussion of off-label use of medication.*

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### References

- Centers for Disease Control and Prevention. Public health and aging: trends in aging—United States and worldwide. *MMWR* 2003;52:101-06.
- Wilson RS, Beckett LA, Barnes LL, et al. Individual differences in rates of change in cognitive abilities of older persons. *Psychol Aging* 2002;17:179-93.
- Park DC, Smith AD, Lautenschlager G, et al. Mediators of long-term memory performance across the life span. *Psychol Aging* 2002;17:621-37.
- Hanninen T, Koivisto K, Reinikainen KJ, et al. Prevalence of aging-associated cognitive decline in an elderly population. *Age Ageing* 1996;25:201-05.
- Albert SA, Michaels K, Padilla M, et al. Functional significance of mild cognitive impairment in elderly patients without a dementia diagnosis. *Am J Geriatr Psychiatry* 1999;7:213-20.
- Zelinski EM, Gilewski MJ, Schaie KW. Individual differences in cross-sectional and 3-year longitudinal memory performance across the adult life span. *Psychol Aging* 1993;8:176-86.
- Small SA, Stern Y, Tang M, et al. Selective decline in memory function among healthy elderly. *Neurology* 1999;52:1392-96.
- Salthouse TA. Mediation of adult age differences in cognition by reduction in working memory and speed of processing. *Psychol Sci* 1991;2:179-83.
- Morrison JH, Hof PR. Life and death of neurons in the aging brain. *Science* 1997;278:412-19.
- Resnick SM, Pham DL, Kraut MA, et al. Longitudinal magnetic resonance imaging studies of older adults: a shrinking brain. *J Neurosci* 2003;23:3295-3301.
- Peterson RC, Jack CR Jr, Xu YC, et al. Memory and MRI-based hippocampal volumes in aging and AD. *Am Acad Neurol* 2000;54:581-87.
- Eriksson PS, Perfilieva E, Bjork-Eriksson T, et al. Neurogenesis in the adult human hippocampus. *Nat Med* 1998;4:1313-17.
- Poirier J, Davignon J, Bouhillier D, et al. Apolipoprotein E polymorphism and Alzheimer's disease. *Lancet* 1993;342:697-699.
- Dik MG, Jonker C, Comijs HC, et al. Memory complaints and APOE-epsilon4 accelerate cognitive decline in cognitively normal elderly. *Neurology* 2001;57:2217-22.
- Ravaglia G, Forti P, Maioli F, et al. Blood homocysteine and vitamin B levels are not associated with cognitive skills in healthy normally ageing subjects. *J Nutr Health Aging* 2000;4:218-22.
- McCaddon A, Hudson P, Davies G, et al. Homocysteine and cognitive decline in healthy elderly. *Dement Geriatr Cogn Disord* 2001;12:309-13.
- Kivipelto M, Helkala EL, Hanninen T, et al. Midlife vascular risk factors and late-life mild cognitive impairment. *Neurology* 2001;56:1683-89.
- Elias PK, Elias MF, D'Agostino RB, et al. Serum cholesterol and cognitive performance in the Framingham Heart Study. *Psychosom Med* 2005;67:24-30.
- Piguet O, Grayson DA, Creasey H, et al. Vascular risk factors, cognition and dementia incidence over 6 years in the Sydney Older Persons study. *Neuroepidemiology* 2003; 22:165-71.
- Li G, Schofer JB, Kukull WA, et al. Serum cholesterol and risk of Alzheimer's disease. *Neurology* 2005;65:1045-50.
- Bernick C, Katz R, Smith NL, et al. Statins and cognitive function in the elderly. *The Cardiovascular Health Study. Neurology* 2005;65:1388-94.
- Yaffe K, Kanaya A, Lindquist K, et al. The metabolic syndrome, inflammation, and risk of cognitive impairment. *JAMA* 2004;292:2237-42.
- Stewart R, Liolita D. Type 2 diabetes mellitus, cognitive impairment and dementia. *Diabet Med* 1999;16:93-112.
- Logroscino G, Knag JH, Grodstein F. Prospective study of type 2 diabetes and cognitive decline in women aged 70-81 years. *Ann Epidemiol* 2003;13:369-76.
- Carmelli D, Swan GE, LaRue A, et al. Correlates of change in cognitive function in survivors from the Western Collaborative Group Study. *Neuroepidemiology* 1997;16:285-95.
- Wilson RS, Mendes de Leon CF, Bennett DA, et al. Depressive symptoms and cognitive decline in a community population of older persons. *J Neurol Neurosurg Psychiatry* 2004;75:126-29.
- Wilson RS, Barnes LL, Mendes de Leon CF, et al. Depressive symptoms, cognitive decline, and risk of AD in older persons. *Neurology* 2002;59:364-70.
- Yaffe K, Blackwell T, Gore R, et al. Depressive symptoms and cognitive decline in nondemented elderly women. *Arch Gen Psychiatry* 1999;56:425-30.
- Jorm AF. History of depression as a risk factor for dementia: an updated review. *Austr N Zealand J Psychiatry* 2001;35:776-82.
- Lupien S, Lecours AR, Lussier I, et al. Basal cortisol levels and cognitive deficits in human aging. *J Neurosci* 1994;14:2893-03.
- Lyketsos CG, Chen L-S, Anthony JC. Cognitive decline in adulthood: an 11.5 year follow-up of the Baltimore Epidemiological Catchment Area Study. *Am J Psychiatry* 1999;156:58-65.
- Albert MS, Jones K, Savage CR, et al. Predictors of cognitive change in older persons: MacArthur Studies of Successful Aging. *Psychol Aging* 1995;10:578-89.
- Chodosh J, Reuben DB, Albert MS, et al. Predicting cognitive impairment in high-functioning community-dwelling older persons: MacArthur Studies of Successful Aging. *J Am Geriatr Soc* 2002;50:1051-60.
- Cagney KA, Lauderdale DS. Education, wealth, and cognitive function in later life. *J Gerontol Psychol Sci* 2002;57B:P163-P172.
- Sherwin BB. Estrogen and cognition in women. *Endocrine Rev* 2003;24:133-51.
- Espeland MA, Rapp SR, Shumake SA, et al: Women's Health Initiative Memory Study. Conjugated equine estrogens and global cognitive function in postmenopausal women: Women's Health Initiative Memory Study. *JAMA* 2004;291:2959-68.
- Resnick SM, Henderson VW. Hormone therapy and risk of Alzheimer's disease: a critical time. *JAMA* 2002;288:2170-72.
- Sherwin BB. Estrogen and memory in women: how can we reconcile the findings? *Horm Behav* 2005;47:371-75.
- Maki PM. Hormone therapy and cognitive function: is there a critical period for benefit? *Neuroscience* 2006;138:1027-30.
- Bagger YZ, Tankó L, Alezandersen P, et al. Early postmenopausal hormone therapy may prevent cognitive impairment later in life. *Menopause* 2005;12:12-17.
- Stampfer MJ, Kang JH, Chen J, et al. Effects of moderate alcohol consumption on cognitive function in women. *N Engl J Med* 2005;352:245-53.
- Colcombe SJ, Kramer AF, Erickson KI, et al. Cardiovascular fitness, cortical plasticity, and aging. *Proc Natl Acad Sci USA* 2004;101:3316-21.
- Schooler C, Mulatu MS. The reciprocal effects of leisure time activities and intellectual functioning in older people: a longitudinal analysis. *Psychol Aging* 2001;16:466-82.
- Vergheze MD, LeValley MA, Derby C, et al. Leisure activities and the risk of amnesic mild cognitive impairment in the elderly. *Neurology* 2006;66:821-27.
- Wang JYJ, Zhou DHD, Li J, et al. Leisure activity and risk of cognitive impairment: the Chongqing aging study. *Neurology* 2006;66:911-13.
- Kramer AF, Bherer L, Colcombe SJ, et al. Environmental influences on cognitive and brain plasticity during aging. *J Gerontol Med Sci* 2004;59A:940-57.
- Koga H, Yuzuriha T, Yao H, et al. Quantitative MRI findings and cognitive impairment among community dwelling elderly subjects. *J Neurol Neurosurg Psychiatry* 2002;72:737-41.
- Coffey CE, Ratcliff G, Bryan RN, et al. Relation of education to brain size in normal aging. *Neurology* 1999;53:189-96.
- Anstey K, Christensen H. Education, activity, health, blood pressure and lipoprotein E as predictors of cognitive changes in old age: a review. *Gerontology* 2000;46:163-77.
- Lindsay J, Laurin D, Verreault R, et al. Risk factors for Alzheimer's disease: a prospective analysis from the Canadian Study of Health and Aging. *Am J Epidemiol* 2002;156:445-53.