ABSTRACT

Alzheimer's disease (AD) is the most common cause of dementia and is present in approximately 4.5 million Americans. AD incurs enormous costs to all stakeholders—the patient, their family, the healthcare community, and society as a whole. Cost-outcome analyses of the currently available drugs to treat AD show that use of these drugs can delay nursing home placement, with perhaps an inadvertent prolonged strain on the caregiver. However, drugs administered early in the disease process can ease caregiver burden and greatly improve quality of life for the patient and caregiver. Several risk factors for AD have been identified and others are emerging. By far, age is the greatest risk factor, followed by family history. AD falls into 2 categories: familial (early onset) and sporadic (late onset). Familial cases usually occur before age 60 years and are caused by inheritance of mutations in 1 or more of 3 genes: PS1 (presenilin 1), PS2 (presenilin 2), and APP (amyloid precursor protein). APOE (apolipoprotein E) is the most studied gene that increases risk for AD in sporadic AD. The ε4 allele of APOE is associated with the highest AD risk, but it is neither necessary nor sufficient for developing AD. This article reviews the current data on other risk factors under investigation (ie, race, hormone therapy in women, and depression), in addition to the role of APOE ε4 in mild cognitive impairment (thought to be a possible precursor or early stage of AD) and other types of cognitive impairment. The challenge for the primary care nurse is to actively look for risk factors in all middle-age patients, then convey the importance of modifying risk factors that can lower risk for AD 10 to 15 years later. (Adv Stud Nurs. 2005;3(6):188-197)
Causes of Dementia lists other common causes of dementia and their frequencies. AD often coexists with vascular dementia (VaD), sometimes referred to as mixed dementia. The presence of VaD or even its risk factors (ie, hypertension, smoking, hypercholesterolemia, diabetes, and cardiovascular and cerebrovascular disease) can complicate the diagnosis of AD. It can be difficult to determine if symptoms are attributable to vascular pathology or AD.

<table>
<thead>
<tr>
<th>Some of the Most Common Causes of Dementia</th>
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<tbody>
<tr>
<td>Alzheimer’s disease</td>
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<tr>
<td>Lewy body dementia</td>
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<tr>
<td>Mixed dementia (AD with vascular dementia)</td>
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<tr>
<td>Depression</td>
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<td>Vascular dementia</td>
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<td>Metabolic disorders</td>
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<td>Drug intoxication</td>
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<td>Infections</td>
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<td>Structural brain lesions</td>
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<td>Dementia secondary to alcohol</td>
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<td>Hydrocephalus</td>
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<tr>
<td>Parkinson’s disease</td>
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<td>Pick’s and other frontal lobe dementias</td>
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Adapted with permission from Corey-Bloom.5

The Cost of Alzheimer’s Disease

Alzheimer’s disease is a devastating disease that exacts a large financial, emotional, and psychological toll on patients and their family members. Yet, the exact cost of AD is difficult to quantify. The costs of caring for a patient with AD are numerous and varied, such as the cost of drugs to treat the symptoms, hospitalization for falls, specialized home care, ultimately nursing home care, hospice care, and cost to caregivers (time, stress, unemployment, and out-of-pocket expenditures). The types of costs change as the disease progresses, as shown in Figure 3. Costs start as unpaid direct care and move to long-term residential care with increasing AD severity. Long-term care costs ultimately constitute most of the costs for AD overall. The extent to which the family pays directly for these costs depends on their specific circumstances.

Costs to the Patients and Caregivers

Patients with AD and their caregivers carry a large economic burden from AD, through direct medical costs or indirect costs of emotional strain and lost social and professional opportunities. According to a report for the Alzheimer’s Association, AD costs American businesses $61 billion per year, of which $36.5 billion covers costs related to caregivers (ie, lost productivity, absenteeism, and worker replacement).2,11

Figure 1. Distribution of AD Cases by Age, Based on the 2000 US Census Data

[Graph showing distribution of AD cases by age group: 65–74 = 7%, 75–84 = 53%, ≥85 = 40%]

AD = Alzheimer’s disease.
Data from Hebert et al.7
More than 70% of patients with AD live at home, with family and friends providing 75% of their care.\textsuperscript{2,12} The remaining costs are for paid care—an average of $19,000 per year, usually paid out of pocket by families.\textsuperscript{2,13} For the person with AD, average lifetime costs are estimated at $174,000.\textsuperscript{2,14}

**Costs to the Healthcare System**

For the US healthcare system, the total direct and indirect costs are estimated to be at least $100 billion (based on 1991 data).\textsuperscript{2,14} The Alzheimer’s Association reports that Medicare costs for beneficiaries with AD are expected to increase 75% from $91 billion in 2005 to $160 billion in 2010, and Medicaid expenditures on residential dementia care will increase 14% from $21 billion in 2005 to $24 billion in 2010.\textsuperscript{2,15} Currently, the average cost for nursing home care is $42,000 per year per patient with AD, which is higher than the costs for other types of dementia.\textsuperscript{2,16} In a recent study of patients with AD in Massachusetts, the cost per patient with AD was $23,436 for informal care and $8064 for formal services (with variations primarily according to the level of assistance needed for instrumental activities of daily living [IADLs]).\textsuperscript{17} The biggest challenge to calculating the cost of AD is determining a cost or monetary value for unpaid caregiver time.

**Cost of Alzheimer’s Disease Medications**

There are currently 4 medications to treat the cognitive symptoms of AD: donepezil, galantamine, rivastigmine (acetylcholinesterase inhibitors, approved for treatment of mild to moderate AD), and memantine (a noncompetitive NMDA receptor antagonist, approved for use in moderate to severe AD). Several cost-outcome analyses have tried to determine if the efficacy of these drugs translates into cost effectiveness. In brief, the drugs show benefit in delaying time to placement in a nursing home and reducing the time required by caregivers in helping patients with activities of daily living (ADLs).\textsuperscript{18,19} Although the cost of the drugs can negate some of these savings, the benefits of maintaining or slowing cognitive decline are numerous and substantial. However, at this time, it is not possible to say definitively whether one drug is more cost effective than another, or if the drugs are truly “cost effective” from a societal point of view.\textsuperscript{20} A frequent concern with treatments that delay nursing home placement is that the caregiver burden is extended. However, with early treatment, increased levels of
patient functioning and cognition can be prolonged, which eases not only caregiver time requirements with the patient but, more importantly, caregiver emotional and psychological burden, and it can increase the time during which patients can enjoy their life as much as possible and put their affairs in order.

As the disease progresses, patients with AD often experience neuropsychiatric symptoms that can cause behavioral disturbances (to be reviewed in Part 2 of this series). The most frequent symptoms are apathy, depression, and agitation/aggression (including wandering), and they are present to some extent in most patients with AD. The severity of these symptoms can vary throughout the course of the disease.21-25 These symptoms contribute greatly to caregiver stress and burden, diminished quality of life for patient and caregiver, excess patient morbidity, and cost of illness. Neuropsychiatric symptoms can account for 33% of the primary caregiver’s hours of unpaid care, in addition to the normal caregiver activities and duties.26

As will be reviewed in Part 3 of this series, drugs are not the only intervention for treating AD symptoms, especially as the disease progresses. Patients with AD benefit from many types of treatments from other disciplines, such as exercise, sensory stimulation, relaxation, and use of music or audiovisual stimulation. There are also costs associated with these treatments because they are administered by nursing home medical staff or practitioners in those respective fields. Services to ease caregiver burden are also becoming more common, such as respite care, foster care, support groups, transportation, meal delivery, and part-time in-home care, all of which also have costs associated with them.10

**RISK FACTORS**

Several risk factors for AD have been identified and others are emerging. Age is the greatest risk factor, followed by family history, but they do not strictly determine who will develop AD. Thus, everyone is at risk for AD to some extent. Regarding family history, those individuals with a parent or sibling with AD are 2 to 3 times more common, such as respite care, foster care, support groups, transportation, meal delivery, and part-time in-home care, all of which also have costs associated with them.10

**GENETICS**

The APOE gene has 3 alleles: e2, e3, and e4. e4 is associated with the highest risk of AD, but it is neither necessary nor sufficient for developing the disease. Approximately 35% to 50% of people with AD have at least one copy of the APOE-e4 allele. Those individuals who are homozygous for APOE e4 have an even higher risk of AD, but homozygosity does not guarantee that AD will develop.22 Data from the Cache County Study (a large Utah county with 5677 elderly) suggest that having the e4 allele reduces the age of maximum prevalence in those patients with AD from 95 years in patients with no e4 alleles to 87 years in heterozygotes and 73 years in homozygotes. Thus, the e4 allele may lower the age of onset of AD.31

New efforts are focusing on what may be the earliest stages of AD or mild cognitive impairment (MCI). Patients with MCI convert to AD at a rate of approximately 10% to 15% per year. As a comparison, the development of dementia in persons not reporting MCI occurs at a rate of approximately 1% to 2% per year.5 However, by 6 years approximately 80% of patients with MCI will convert to dementia.7 The relationship between APOE e4 and MCI is not yet clearly defined, but data from the Religious Orders Study...
suggest that possession of the e4 allele increases the risk of AD (to nearly double) in those patients with MCI.34 The Religious Orders Study is a collaborative study with Rush University Medical Center (and several other US medical centers) and more than 1000 older, religious clergy (nuns, priests, and brothers) who have agreed to medical and psychological evaluation each year and brain donation after death.35

Another group of cognitively impaired patients have been studied. “Cognitive impairment, no dementia” (CIND) is defined as some degree of cognitive impairment on clinical examination and neuropsychological testing, which does not meet the criteria for dementia. (Many people include CIND under the rubric of MCI.) In one study, APOE e4 was a significant risk factor for converting from CIND to AD (odds ratio [OR] 2.69, 95% confidence interval [CI], 1.48–4.92) and was associated with decreased age of AD onset.36

With the discovery of the APOE-e4 allele and its relationship to AD risk, patients and their family members may express an interest in genetic testing. However, the Ethics Committee of the American Geriatrics Society states that genetic testing for later-onset (ie, sporadic) AD should not become standard care but should be considered on an individual basis. In most cases, the results will not affect treatment decisions, and positive results among family members can evoke strong and devastating reactions, in addition to possible restrictions in job opportunities or insurance coverage.37 Goldman and Hou provide a checklist of questions that the patient and their family members should consider before genetic testing for dementia (see “Questions Each Patient and Family Member Should Consider Before Diagnostic Genetic Testing for Dementia” sidebar) and a comparison of presymptomatic versus diagnostic testing and the information each provides (Table).38 Until the exact relationship between possession of an e4 allele and AD is described, genetic testing is not recommended for the general population and, if it is carried out, it should be performed only after thorough genetic counseling.

**Gender and Hormone Therapy**

Women appear to be at higher risk of AD, even after accounting for longer life spans and the larger number of elderly women compared to men.39 The role of estrogen and hormone replacement therapy (HRT) in the risk or prevention of AD has become controversial, especially when the results of the Women’s Health Initiative (WHI) were published. Observational studies had suggested that HRT may protect postmenopausal women against AD, but randomized controlled trials refuted those ideas. The WHI Memory Study compared the rates of dementia or cognitive decline in women taking HRT as estrogen plus progestin or estrogen-only replacement therapy versus placebo. Neither hormone therapy protected against cognitive decline, and HRT may have even increased the risk.40,41 Some researchers have suggested that the type of hormone therapy (eg, different doses and different sources of estrogen or progestin) or time of the treatment (ie, postmenopausal vs perimenopausal) may affect the risk of cognitive decline.42–44 Thus, when older female patients inquire about using or continuing HRT to avoid AD, the nurse needs to counsel the patient that the decision whether to use HRT, which kind of HRT, and for how long should be based on clinical factors relating to her menopause and her medical history (eg,
family history of breast cancer), not on any possible effect on future cognitive decline.

**Social and Mental Stimulation**

One of the most interesting findings in recent years is the possible role of social and mental stimulation in predicting risk of future AD. The Alzheimer's Disease Case Control Study at Case Western Reserve University studied the effect of participating in 26 nonoccupational activities (classified as passive, intellectual, and physical) throughout early (ages 20–39 years) and middle (ages 40–60 years) adulthood on AD development. The results showed that the controls (ie, those individuals not having AD) were more active during mid-life than the cases, in both diversity (different types of activities) and intensity (number of hours per month). If participation increased from early to middle adulthood, the probability of AD decreased significantly, and those individuals who performed less than the mean value of activities had a 3.85 higher risk of AD than those people who performed at least the mean levels (95% CI, 2.65–5.58; P <.001).45

There are other surrogate markers of lower mental stimulation, such as television watching. Lindstrom et al showed that for each additional daily hour of middle-adulthood television viewing, the risk of AD increased 1.3 times (controlling for year of birth, gender, income, and education).46 As reviewed by Scarmeas and Stern, some researchers have suggested that participation in mentally stimulating activities forms more efficient cognitive networks, thus creating a "cognitive reserve."47,48 This cognitive reserve may delay onset of AD or permit a greater tolerance for AD pathology.47,48

**Race**

African Americans are known to have a higher risk of AD than whites, but they also possess many of the risk factors for VaD, thus AD may not be fully diagnosed in this population. Importantly, the Alzheimer's Association indicates that African Americans tend to be diagnosed at a later stage, limiting the effectiveness of any treatments for the disease symptoms, and that the age-specific prevalence of dementia is 14% to 100% higher in African Americans than in whites.49 There appear to be improvements in recognizing AD in this population. The number of African Americans with AD is reported to have nearly doubled during the years 1991 to 1999. The increase was particularly strong in African-American women, in whom the rate increased by 4.7-fold compared to 2.3-fold for white women. In fact, African Americans had a higher rate of identified AD in 1999 than whites (62.5/1000 vs 40.9/1000), a reversal of rates from 1991 (13.7/1000 vs 16.5/1000), based on Medicare databases. The authors suggest that the causes of this increase are probably multifactorial. For example, during this time period, African Americans had

### Table. Comparison of Presymptomatic and Diagnostic Genetic Testing for Alzheimer's Disease

<table>
<thead>
<tr>
<th>Presymptomatic Testing</th>
<th>Diagnostic Testing</th>
</tr>
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<tbody>
<tr>
<td><strong>Testing for autosomal dominant predisposition genes: PS1, PS2, APP</strong></td>
<td>Clinical testing of PS1 and PS2; research testing of APP; known family mutation required; genetic counseling required</td>
</tr>
<tr>
<td><strong>Testing for susceptibility genes: APOE</strong></td>
<td>Clinical testing not recommended; research testing without results available</td>
</tr>
<tr>
<td><strong>Interpretation of predisposition gene test result (PS1, PS2, and APP)</strong></td>
<td>Mutation found: near 100% lifetime risk; no mutation found: population risk of AD</td>
</tr>
<tr>
<td><strong>Interpretation of APOE test</strong></td>
<td>APOE 3 or 4: 3–5 times lifetime risk for AD; APOE 4 (homozygous): 8–18 times lifetime risk</td>
</tr>
<tr>
<td><strong>Indication for genetic testing for predisposition genes</strong></td>
<td>Known mutation in family</td>
</tr>
<tr>
<td><strong>Indication for genetic testing for APOE</strong></td>
<td>None</td>
</tr>
</tbody>
</table>

| AD = Alzheimer’s disease; APOE = apolipoprotein E; APP = amyloid precursor protein; PS1 = presenilin 1; PS2 = presenilin 2. Adapted with permission from Goldman and Hou. Alzheimer Dis Assoc Disord. 2004;18:65-67. |
improved access to healthcare and there was increased sensitivity among healthcare practitioners and the general public to AD in African Americans (i.e., that its symptoms are not a normal part of aging). Also, changes in ICD-9 coding rules allowed for identification of patients with AD when they also had risk factors for VaD, such as prior stroke, which is more common among African Americans than whites.50

**Physical Activity**

Physical activity appears to improve cognitive functioning, implying that lack of physical activity may be a risk factor for AD. Animal studies have shown that exercise can help with cognitive function through several processes: preserving “neural plasticity” (i.e., ability of neural circuits to undergo changes in function or organization as a result of a particular activity), increasing levels of brain-derived neurotrophic factor (which increases neuronal survival, enhances learning, and protects against cognitive decline), and decreasing the number of plaques (a histopathologic hallmark of AD) in the brain.51,52

In humans, 2 large studies have shown that physical activity decreases the risk of developing AD. In the Canadian Study of Health and Aging, 4615 adults aged at least 65 years were followed for 5 years and screened for AD (or other types of dementia) at endpoint. The results showed that the OR for AD decreased with increased physical activity at baseline when adjusted for age, gender, and educational level. With high levels of physical activity, the OR for AD was 0.50 (95% CI, 0.28–0.90; \(P = .02\)). The trend continued when analyzed by gender, but it was significant only for women. When the data were adjusted for age and educational level only, the OR for AD with high physical activity was 0.38 (95% CI, 0.16–0.91). When the data were adjusted for age, gender, educational level, smoking, alcohol, use of nonsteroidal anti-inflammatory drugs, functional ability in ADLs and IADLs, self-rated health, and the number of chronic health conditions, the OR was 0.27 (95% CI, 0.08–0.90 for high physical activity; \(P = .05\)).53 A more recent study analyzed physical activity along with APOE genotype as a risk factor for AD, VaD, or all-cause dementia, as part of the Cardiovascular Health Cognition Study (a population-based, prospective study involving adults aged 65 years designed to identify cardiovascular risk factors).54 In this study of 3608 adults without dementia, 480 developed dementia during the 5.4 years of follow-up. The amount of energy expended during physical activity (in kcal/week) and the number of activities in the 2 previous weeks were recorded and analyzed, along with several other known and suspected risk factors of AD. The results show an inverse relationship between physical activity and dementia risk. Those individuals who had the greatest energy expenditure (>1657 kcal/week) in physical activity were significantly younger, male, white, more highly educated, of normal body mass index, had fewer comorbid conditions (congestive heart failure, diabetes, or hypertension), had less physical difficulty with ADLs and IADLs, less depression, increased number of activities in the previous 2 weeks, alcohol intake of at least 1 drink/week, an estrogen replacement therapy user (female participants were more likely to be on estrogen replacement therapy), and had fewer white matter lesions as measured with magnetic resonance imaging (MRI). They also had higher scores on cognitive tests. Factors that were not associated with greater energy expenditure were comorbidities of stroke or transient ischemic attack or congestive heart failure, current smoking, low high-density lipoprotein cholesterol and high low-density lipoprotein cholesterol, possession of the APOE-ε4 allele, and carotid maximum intima-media thickness. Walking and household chores were the most common activities reported. Hazard ratios for all-cause dementia based on degree of energy expenditure (in kcal/week) were significantly lower with increased activity and number of activities, even when adjusted for age (Figures 4 and 5). Of note, the relationship between energy expenditure and multivariate hazard ratio for dementia or AD was not statistically significant when adjusted for age, educational level, gender, ethnicity (white or nonwhite), APOE genotype (ε4 or non-ε4), cognitive functioning test scores, MRI evidence of white matter lesions, impairment of ADLs or IADLs, or measures of social contact and social support, but it maintained the trend. The relationship between the number of activities and multivariate hazard ratio for dementia or AD was significant. Overall, the significant inverse relationship between physical activity and all-cause dementia risk was limited to APOE-ε4 noncarriers; these associations were similar for AD. Thus, benefit of physical activity in reducing the risk of AD appears to be independent of the APOE genotype.55
**Other Possible Risk Factors**

More recently, depression and other factors are also being evaluated for a role in AD onset. Depression is a known, frequent comorbid condition with AD that can sometimes mask diagnosis of AD. Two other studies have analyzed multiple risk factors for AD. Lindsay et al showed that use of nonsteroidal anti-inflammatory drugs, wine consumption, coffee consumption, and regular physical activity were associated with a reduced risk of AD, whereas family history of dementia, gender, history of depression, estrogen replacement therapy, head trauma, antiperspirant or antacid use, smoking, high blood pressure, heart disease, or stroke were not associated with AD—conflicting with other reports on some of these risk factors. Specifically, head trauma may also be a risk factor because it can produce diffuse plaques in the brain, similar to those seen with AD. Tyas et al showed that increasing age, fewer years of education, history of migraines (especially in women), and self-reported memory loss at baseline increased the risk of AD, whereas vaccinations and occupational exposure to excessive noise reduced the risk of AD.

Clearly, the causes of AD are numerous and perhaps interconnected, but healthy diet, regular exercise, normal homocysteine level, and mental stimulation are modifiable risk factors, the benefits of which extend well beyond reducing the risk of AD. The challenge for a primary care nurse is not only to identify those individuals at risk for AD, but also educate a middle-aged patient on their risk factors for AD and convince them that modifying some of those risk factors now will reduce their risk for dementia in the next 15 to 20 years. The lifestyle choices they are making now can impact their future health in retirement.

**Conclusions**

With the large baby-boomer population preparing to retire, the number of patients with AD in the United States is poised to increase substantially. The costs of AD are difficult to quantify, but the direct medical care costs can be staggering, particularly because some portion of them often has to be paid out of pocket by the patient or their family/caregivers. Studies are also...
showing that the costs extend well beyond direct medical care for the patient with AD, inflicting extraordinary caregiver burden as disease progresses. The 4 currently available drugs for AD help to maintain cognitive and functional levels, which improves quality of life for the patient and family. Although we cannot yet say with certitude that a particular drug or any of the drugs is “cost effective,” these drugs, along with drugs to treat the neuropsychiatric symptoms, play a critical role in managing AD throughout the disease process. Numerous risk factors have been identified for sporadic AD (the most common form), some of which are modifiable (e.g., serum cholesterol levels, exercise and mental stimulation activities, and possibly consumption of certain other products, such as nonsteroidal anti-inflammatory drugs, wine, or coffee). The primary care nurse should seek to identify risk factors in all middle-aged patients (not just the elderly) and engage in frank discussions with each patient about his or her modifiable risk factors, lifestyle choices, and future health outlook.

REFERENCES

1. 1991 Gallup survey of 1015 individuals (as reported by reference 3).