

# The Growing Burden of Alzheimer's Disease

Oscar L. Lopez, MD

**D**ementia is defined as loss of cognitive function sufficient to interfere with social and occupational functioning. Alzheimer's disease (AD) is the most frequent form of dementia in the elderly. The *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV)* criteria for AD require the presence of progressive deficits in at least 2 cognitive domains, 1 of which should be memory, which are not related to any other disease process.<sup>1</sup> The cognitive deficits must represent a change from a previous state of normal functioning. These changes must be distinguished from acute or subacute confusional states or delirium (eg, metabolic encephalopathy). However, the concept of dementia has been gradually changing. The recent National Institute on Aging/Alzheimer's Association criteria for dementia require impairments in 2 cognitive domains for the diagnosis of dementia, not necessarily in memory functions.<sup>2</sup> These new criteria are oriented to identify dementia syndromes that do not present with memory deficits (eg, frontotemporal dementia). Similarly, the new criteria for vascular dementia proposed by the American Heart Association also require the presence of deficits in 2 cognitive domains, regardless of the presence of memory functions.<sup>3</sup>

## Epidemiology of AD

AD is the most frequent form of dementia in the elderly. The prevalence and incidence of dementia is relatively low in patients 60 to 65 years of age, but there is an exponential increase with age,<sup>4,5</sup> reaching almost 50% in those 85 years of age.<sup>6</sup> After 90 years of age, the incidence of AD climbs dramatically. Corrada and colleagues examined incidence of dementia in a population aged 90+ years, and found that dementia incidence increased exponentially with age, from 12.7% per year in the 90- to 94-year-old age group, to 21.2% per year in the 95- to 99-year-old age group, and to 40.7% per year in those at least 100 years old.<sup>7</sup> This underscores the significant public health burden of AD in the aging population.

In the United States, an estimated 5.2 million people at least 65 years of age have dementia. This number is expected to nearly triple in the next 40 years (**Figure 1**)<sup>8</sup>; the number of cases and the projected prevalence are similar in Europe and worldwide.<sup>9,10</sup> This will have a tremendous impact on society and medical systems. A study on disability conducted by Sousa and colleagues in elderly people in several countries found that dementia, not blindness, was

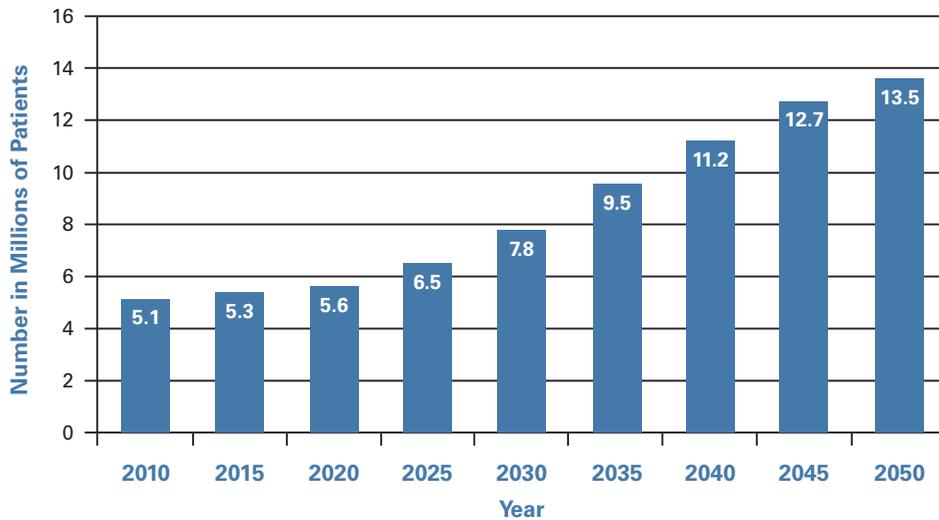
## Abstract

Most dementias in people at least 65 years of age are attributable to Alzheimer's disease (AD). While approximately 5.4 million Americans are now believed to have AD, the AD population is expected to nearly triple over the next 40 years, reaching approximately 13.5 million. Presently, there is no cure for AD, but a 2-year delay in AD onset would reduce the expected prevalence by 1.94 million within 50 years. The most important risk factor for AD is age, followed by presence of the apolipoprotein E-4 allele. Other risk factors for AD include sex (female), history of head trauma, family history of Down syndrome or dementia, and cerebrovascular risk factors. The initial neurodegenerative process that causes AD is unknown. However, it is accepted that the presence of amyloid plaques, neurofibrillary tangles, neuronal loss (and synapses), and cerebral amyloid angiopathy are the central pathogenic events. There is selective vulnerability of the limbic system and heteromodal association areas in AD pathology. The most affected neurotransmitter in AD is acetylcholine, as enzymes that are part of its metabolic pathway are depleted. The clinical presentation of AD is heterogeneous and insidious, and the psychological and financial effects of AD on caregivers and family members are significant.

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For author information and disclosures, see end of text.

■ **Figure 1.** Americans 65 Years and Older With AD—2010 Through 2050<sup>8</sup>



AD indicates Alzheimer's disease.

the most important contributor to disability in the elderly.<sup>11</sup> In addition, dementia contributed 10.2% of years of disability in people aged at least 65 years—more than stroke, musculoskeletal disease, or cancer.<sup>11</sup>

Patients with dementia usually overwhelm healthcare services, and a study conducted in the United Kingdom showed that in 2002, 205,000 elderly people with cognitive impairments lived in institutions, with an associated cost of £5.4 billion per year.<sup>12</sup> The estimated worldwide cost of dementia is \$604 billion (2010 US dollars); if dementia were a country, it would be the 18th largest economy in the world.<sup>13</sup> In the United States, the estimated cost of AD is \$183 billion, and it is a significant emotional and financial burden on patients' caregivers, who sacrifice time and effort to care for their loved ones. The cost of informal care is valued at an estimated \$202 billion per year.<sup>8</sup> While the majority of Americans with dementia (an estimated 70%-90%)<sup>13</sup> live at home or with a caregiver, over 230,000 people with AD live in nursing homes, and comprise approximately 15% of the nursing home population.<sup>14</sup>

The progressive nature of AD, leading to severe functional and cognitive deterioration<sup>15</sup> and increased comorbid disease,<sup>16</sup> is one of the major determinants of institutionalization<sup>17</sup> and mortality in the elderly.<sup>18,19</sup> Consequently, the magnitude of this devastating disease has a significant impact on caregivers and healthcare systems and their resources.

### Delay in AD Onset Can Significantly Impact Prevalence

At present, there is no cure for AD; however, the impact of this disease can be lessened by delaying its onset. Brookmeyer

and colleagues suggested more than 12 years ago that an intervention occurring in 1997 and delaying AD onset by 5 years would result in a 50% reduction in the incidence of AD. Furthermore, it would reduce expected prevalence by 1.15 million patients after 10 years (year 2007), and 4.04 million after 50 years (year 2047).<sup>20</sup> A 2-year delay in AD onset would reduce expected prevalence by 1.94 million within 50 years. In the broadest sense of reducing impact on the healthcare system, even much smaller delays in disease onset would be significant. An onset delay of 1 year would reduce prevalence by 210,000 and 770,000 after 10 and 50 years of intervention, respectively. Likewise, an onset delay of 6 months would result in a reduced prevalence of 100,000 and 380,000 after 10 and 50 years of intervention, respectively.<sup>20</sup> This emphasizes the importance of having medications that can be used as primary or secondary prevention treatments. Unfortunately, all large prevention trials conducted to date have not been able to modify the incidence of AD in mild cognitive impairment<sup>21-23</sup> or in cognitively normal subjects.<sup>24</sup>

### Risk Factors and Deterrents for AD

Increasing age and presence of the apolipoprotein E-4 (APOE-4) allele are the two AD risk factors that we can speak of with a high degree of certainty.<sup>25</sup> Kuller and colleagues investigated risk factors for incident dementia (AD alone or in combination with other disease processes represented 85% of the 480 incident cases) in 3608 Cardiovascular Health Cognition Study participants who had magnetic resonance imaging (MRI) of the brain in 1991 and were followed through 1999. The hazard ratios for age (1.1), cognitive

measures (0.9), MRI findings (ventricular size [1.4], white matter lesions [1.8], infarcts >3 mm [0.3]), and APOE-4 (2.6) indicated that these variables were significant predictors of dementia. The combination of APOE-4 genotype, cognitive measures, and greater ventricular size or white matter lesions at baseline MRI (1991-1994) were associated with a 17-fold greater risk of dementia in 1998 to 1999 compared with participants without these attributes.<sup>26</sup>

Other possible risk factors for AD include female sex,<sup>6</sup> education level (or cognitive reserve),<sup>27</sup> head trauma,<sup>28</sup> family history of Down syndrome or dementia,<sup>29</sup> and cerebrovascular risk factors (eg, hypertension, diabetes mellitus).<sup>30,31</sup> The association between white matter lesions, ventricular size, and cerebral infarcts as risk factors for AD suggested a long-term effect of hypertension and diabetes mellitus on the brain vasculature, and some studies have indicated that the vascular process associated with AD starts in midlife.<sup>32</sup> Possible deterrents to the development of AD and related dementias include moderate consumption of alcohol (eg, red wine),<sup>33</sup> a Mediterranean diet,<sup>34</sup> and physical<sup>35</sup> and cognitive activities.<sup>36,37</sup>

### Age Is a Risk Factor for AD

Assuming that age is the most significant AD risk factor, it is important to appreciate that aging and AD affect the brain concurrently. Volumetric 3-dimensional MRI studies have found that aging lowers gray matter volume in the sensorimotor and heteromodal association areas in the parietal, occipital, temporal, and frontal lobes, and in the cerebellum.<sup>38</sup> Atrophy with age is also seen in the hippocampus, thalamus, and middle cingulate gyrus. Therefore, aging increases brain vulnerability to AD.

### Structural Lesions and Biochemical Dysfunction in AD

The lesions and biological dysfunction associated with AD occur on a microscopic level and are not observable through simple MRI or computed tomography. The characteristic pathologic process in AD is defined by the presence of deposits of senile neuritic plaques (SNPs)<sup>39</sup> and neurofibrillary tangles (NFTs),<sup>40,41</sup> with degeneration of the neurons and synapses,<sup>42-44</sup> especially in the limbic and paralimbic regions. NFTs are found in nerve cell bodies and are formed of paired helical filaments which largely consist of hyperphosphorylated tau proteins. Tau proteins are essential components of neurons and are associated with axonal microtubular integrity. In neurodegenerative processes, tau proteins can hyperphosphorylate, increasing the propensity to oligomerize and accumulate as paired helical filaments, and eventually

form insoluble aggregates. NFT pathology appears to start in the entorhinal/hippocampal region and gradually encompass other cortical areas.<sup>40,41</sup>

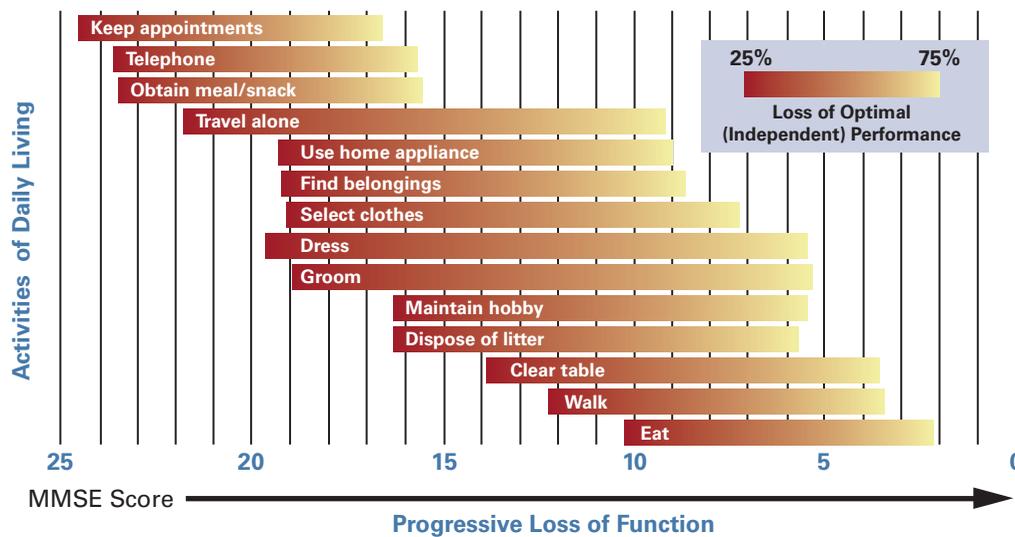
SNPs are mainly formed of A $\beta$ -amyloid proteins<sup>45</sup> and they are considered the central pathological process in AD. Indeed, it has been hypothesized that pathologic metabolism of the amyloid precursor protein is the initial event, which later leads to aggregation of A $\beta$ -amyloid proteins to form SNPs.<sup>46</sup> Therefore, aggregation of A $\beta$ -amyloid proteins leads to the formation of NFTs, loss of synaptic activity, and neuronal loss, although some studies have shown that soluble A $\beta$  oligomers can alter neuronal function, even before the SNP has formed.<sup>47</sup> A $\beta$ -amyloid proteins are also deposited in the walls of brain vessels, leading to cerebral amyloid angiopathy. It is difficult to determine where the amyloid deposits start to accumulate. However, neuroimaging studies using amyloid ligands have shown that the frontal lobes and the superior parietal and posterior cingulate gyrus cortices are the earliest brain regions affected by amyloid pathology.<sup>48,49</sup> AD pathology can also be associated with Lewy bodies in up to 60% of cases,<sup>50</sup> and with other pathological mechanisms, including vascular disease, cell cycle abnormalities, inflammation, oxidative stress, and mitochondrial dysfunction.

The loss of neurotransmitter function in AD is closely associated with the pathological changes. The cholinergic system is especially vulnerable in AD; up to 90% of the cholinergic neurons in the nucleus basalis of Meynert disappear,<sup>51,52</sup> which is the main source of acetylcholine (ACh) in the neocortex. On the other hand, the cholinergic nuclei in the brain stem remain relatively intact. The loss of ACh is proportional to the loss of the enzyme involved in its synthesis, choline acetyltransferase (ChAT), and the loss of ChAT activity correlates with cognitive function and severity of AD.<sup>53</sup> Other neurotransmitters associated with AD are serotonin, norepinephrine,<sup>54</sup> and glutamate.<sup>55</sup> Although patients with AD can have extrapyramidal signs, the dopaminergic neurons remain relatively intact in the substantia nigra.<sup>56</sup>

### Gradual Loss of Cognition and Function

AD is a progressive neurodegenerative disease that leads to the loss of memory, naming and language, visuospatial-visuoconstructional, and frontal/executive functions. The memory loss appears early in the course, while immediate memory is preserved, as is the ability to recall things from the more distant past ("remote memory"). These deficits and their sequence correlate somewhat with the origins of the pathology of the disease; NFTs appear initially in the mesial temporal lobe and spread from there.<sup>40,41</sup> On positron emission tomography and in amyloid ligand studies, the earliest

■ **Figure 2.** Progressive Loss of Function in AD<sup>64</sup>



AD indicates Alzheimer’s disease; MMSE, Mini-Mental State Exam.

changes in glucose metabolism are in the precuneus and posterior cingulate gyrus<sup>57,58</sup>; these brain regions are also related to episodic memory function.<sup>59</sup>

Although memory loss is usually the initial and most prominent problem, deficits in cognitive domains other than memory can occur in the early stages of disease in some patients. Frontal,<sup>60</sup> occipital,<sup>61</sup> or executive function deficits<sup>62</sup> may be the most prominent initial symptoms in AD. In addition, in a small number of patients, memory may be relatively preserved in the early stages of AD. Becker and colleagues examined 191 patients with probable AD and found that 79% had both verbal and visual memory deficits at baseline, 7% had only verbal memory difficulties, and 6% had only visual memory impairment. Interestingly, 7% of the subjects had memory performance in the normal range, although they later exhibited both visual and verbal memory impairment.<sup>63</sup>

The cognitive progression of AD parallels that of activities of daily living (ADL). In studying functional decline, Galasko and colleagues found 27 widely applicable ADL associated with cognitive decline (Figure 2).<sup>64</sup> Final deterioration leads to a bedridden, mute, incontinent, and unresponsive state, which mimics the persistent vegetative state. Life expectancy of patients with AD is significantly less than that predicted by life tables, with a general range of 4 to 12 years from onset, and depending on the age when symptoms began.<sup>18</sup> The coexistence of vascular disease with AD increases the risk of death.<sup>65</sup>

### Behavioral Symptoms in AD

Families frequently say that they can live with the memory and other cognitive deficits of their loved ones, but that the behavioral (eg, psychosis, aggression, and agitation) and mood-related symptoms (eg, depression) are much more difficult to handle. Psychotic symptoms (eg, hallucinations, delusions), wandering, aggressive behavior, and psychomotor agitation are common in AD.<sup>63-69</sup> Not all patients with AD, however, have these abnormal behaviors. It has been suggested that these behaviors are associated with specific phenotypes with a different natural history, and they may have a genetic component.<sup>70,71</sup>

The frequency of depressive symptoms (eg, sadness, anhedonia, anergia, anxiety, depressed mood) is common in AD,<sup>66,72,73</sup> and they occur in up to 86% of patients. However, syndromal major depression by DSM-IV criteria is less common and likely occurs in less than 15% of patients.<sup>66,74</sup> Further, the prevalence of major depression tends to decrease in the late stages of AD.<sup>73</sup> It has been suggested that depression associated with AD may be a direct result of neurological damage rather than a psychological reaction to the disease.<sup>75-77</sup> Patients with AD and depression have more frontotemporal-subcortical (eg, aminergic nuclei) pathology.<sup>78-81</sup> In addition, patients with the Lewy body variant of AD have more depression than those with AD alone, especially when the Lewy bodies are localized in the amygdala.<sup>82</sup> The presence of major depression can increase the risk of death in patients with AD,<sup>83</sup> although this has not been a consistent finding.<sup>15,84,85</sup>

Psychotic symptoms (hallucinations and delusions) are also common in AD; they are present in more than 30% of cases at some point.<sup>66,86,87</sup> Importantly, psychotic symptoms are predictors of more rapid disease progression and nursing home admission.<sup>15,88,89</sup> Neuroimaging studies showed that psychosis was associated with greater involvement of the temporal and frontal lobes,<sup>90-95</sup> and neuropathological studies have shown that there is greater AD pathology in the frontal-temporal areas in patients with psychosis.<sup>96</sup> Interestingly, genetic studies suggest there are genetic influences associated with this behavioral phenotype. In a study conducted by the National Institute of Mental Health's Alzheimer's Disease Genetic Initiative, siblings (with AD) of patients with AD and psychosis had higher psychosis rates compared with those who had AD and no psychotic symptoms.<sup>71,97,98</sup>

Agitation and aggression are disturbing symptoms in patients with AD. Neuroimaging studies have shown that there is greater orbitofrontal-frontal dysfunction in these patients.<sup>92,95</sup> Longitudinal studies have shown that agitation and aggression result in more rapid nursing home admissions in patients with AD.<sup>15,99</sup> These abnormal behaviors usually lead to increased use of psychiatric medications and caregiving time, and consequently have a significant impact on the medical system and society in general.

### The Psychological Impact of AD on Family and Caregivers

The stress of caregiving for a family member with AD, or even just living with an AD-stricken family member, is obviously high. Tests such as the Neuropsychiatric Inventory (NPI) and NPI Caregiver Distress Scale accurately reflect which symptoms, and how varied symptom severities, impact caregivers of patients with AD.<sup>100</sup> Agitation, dysphoria, irritability, delusions, and apathy affect caregivers the most. Caregiver distress is typically more strongly associated with neuropsychiatric alterations than cognitive symptoms.<sup>101</sup>

### Conclusions

The prevalence of AD increases with age, including in those greater than 90 years of age. By the year 2050, the incidence of AD in the United States is expected to be 13 million. Age is the most significant AD risk factor known to date. The etiology of AD remains unknown; however, amyloid metabolism may play a crucial role in the pathophysiology of AD. The presentation and progression of AD is heterogeneous. Psychiatric features are highly prevalent in AD, and their expression severely impacts family and caregivers.

**Author affiliations:** University of Pittsburgh, Pittsburgh, Pennsylvania.

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**Address correspondence to:** Oscar L. Lopez, MD, 3500 Forbes Ave, Ste 830, Pittsburgh, PA 15213. E-mail: lopezol@upmc.edu.

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