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Epidemiology of Alzheimer Disease

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The global prevalence of dementia has been estimated to be as high as 24 million, and is predicted to double every 20 years until at least 2040. As the population worldwide continues to age, the number of individuals at risk will also increase, particularly among the very old. Alzheimer disease is the leading cause of dementia beginning with impaired memory. The neuropathological hallmarks of Alzheimer disease include diffuse and neuritic extracellular amyloid plaques in brain that are frequently surrounded by dystrophic neurites and intraneuronal neurofibrillary tangles. The etiology of Alzheimer disease remains unclear, but it is likely to be the result of both genetic and environmental factors. In this review we discuss the prevalence and incidence rates, the established environmental risk factors, and the protective factors, and briefly review genetic variants predisposing to disease.

Alzheimer disease is characterized by progressive cognitive decline usually beginning with impairment in the ability to form recent memories, but inevitably affecting all intellectual functions and leading to complete dependence for basic functions of daily life, and premature death. The pathological manifestations of Alzheimer disease include diffuse and neuritic extracellular amyloid plaques and intracellular neurofibrillary tangles accompanied by reactive microgliosis, dystrophic neurites, and loss of neurons and synapses (see Serrano-Pozo et al. 2011). While these pathological lesions do not fully explain the clinical features of the disease, it has been hypothesized that alterations in the production and processing of amyloid β-protein may be the principal initiating factor. The underlying causes of these multifaceted changes remain unknown, but advancing age, and genetic and nongenetic antecedent factors are thought to play important roles. Alzheimer disease is the most frequent cause of dementia in Western societies. In the US, approximately 5.5 million people are affected, and the prevalence worldwide is estimated to be as high as 24 million. Given that both established and developing nations are rapidly aging, the frequency is expected to double every 20 years until 2040. The magnitude of the impending rise owing to societal aging is considerable and will be a costly public health burden in the years to come.

DEFINITIONS AND CRITERIA

In 1984, representatives from the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer Disease and Related Disorders Association (NINCDS-ADRDA) developed a uniform set of criteria

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to enable clinicians and researchers to maintain consistency in the diagnosis. They included aspects of medical history, clinical examination, neuropsychological testing, and laboratory assessments (McKhann et al. 1984). These criteria have been remarkably reliable and valid for the diagnosis of AD over the past three decades (Galasko et al. 1994; Lim et al. 1999). The criteria were developed with the intent of accurately associating the clinical symptoms with the neuropathological manifestations after death. Levels of certainty were established that were labeled as *definite* for autopsy-confirmed disease, *probable* for the typical clinical syndrome without intervening issues and *possible* for diagnoses complicated by disorders that might contribute to the dementia. The criteria facilitated estimates of the prevalence and incidence rates of clinically diagnosed probable and possible AD.

The NINCDS-ADRDA criteria have very recently been updated (McKhann et al. 2011). With major advances in neuropsychological assessment, brain imaging and the neuropathological, biochemical and genetic understanding of this disease, revisions were considered a necessity. The breadth of the AD phenotype in society is greater than was previously thought. For example, neuropathological changes may precede clinical dementia by a decade or more. The growing use of brain imaging and cerebrospinal fluid biomarkers (see below) may yield both higher specificity and sensitivity in the diagnosis and thus are considered in the updated diagnostic criteria, especially when used for clinical research. It has become increasingly clear that cerebrovascular disease can coexist with AD to a greatly varying extent, further contributing to the cognitive and physical dysfunction.

A set of newly proposed criteria are similar to, but distinct from, those in the 1984 NINCDS-ADRDA criteria, with updates that include the recognition of both amnestic and nonamnestic symptom onset and alterations in numerous other cognitive domains. Further, cerebrovascular disease is now recognized as a contributor to dementia, defined by a history of a stroke temporally related to the onset or worsening of cognitive impairment, the presence of multiple or extensive infarcts, or severe burden of hyperintense white matter lesions by MRI. Accordingly, the presence of substantial cerebrovascular pathology reduces the certainty of a clinical diagnosis of AD to possible. Hallucinations, delusions, Parkinson-like motor manifestations and realted findings can suggest dementia with Lewy bodies or other forms of dementia (see Tarawneh and Holtzman 2011; Weintraub et al. 2011).

In this chapter, we will discuss the prevalence and incidence rates of AD disease in developed and developing countries and summarize the evidence for numerous antecedent risk factors, protective factors and genetic risk factors.

FREQUENCY OF ALZHEIMER DISEASE

In 2005, Alzheimer Disease International commissioned an international group of experts to reach a consensus on dementia prevalence and estimated incidence in 14 World Health Organization regions, based on epidemiological data acquired over recent years. The results suggested that 24.2 million people lived with dementia at that time, with 4.6 million new cases arising every year (Ferri et al. 2005). North America and Western Europe have at age 60 the highest prevalence of dementia (6.4 and 5.4% of the population at age 60), followed by Latin America (4.9%) and China and its developing western-Pacific neighbors (4.0%). The annual incidence rates (per 1000) for these countries were estimated at 10.5 for North America, 8.8 for Western Europe, 9.2 for Latin America and 8.0 for China and its developing western-Pacific neighbors, increasing exponentially with age in all countries, especially through the seventh and eighth decades of life.

The prevalence rates for AD also rise exponentially with age, increasing markedly after 65 years. There is almost a 15-fold increase in the prevalence of dementia, predominately Alzheimer disease, between the ages of 60 and 85 years (Evans et al. 1989). Compared with Africa, Asia and Europe, the prevalence of AD appears to be much higher in the US, which may relate to methods of ascertainment. The prevalence may be higher among African-American and

Hispanic populations living in the US, but lower for Africans in their homelands, for reasons that remain uncertain (Ogunniyi et al. 2000; Hendrie et al. 2001).

In 1998, Brookmeyer et al. estimated the age-specific incidence rates of AD based on studies in Boston, Framingham, Rochester, and Baltimore. These rates doubled every 5 years after the age of 60 and rose from about 0.17% per year at age 65 to 0.71, 1.0, and 2.92% per year, respectively, at 75, 80, and 85 (Brookmeyer et al. 1998). This observation is consistent with the vast majority of studies that have estimated the age-specific incidence of AD by sex and by ethnic group (Fig. 1; Bachman et al. 1993; Letenneur et al. 1994; Brayne et al. 1995; Hebert et al. 1995; Aevarsson and Skoog 1996; Fratiglioni et al. 1997; Andersen et al. 1999; Copeland et al. 1999; Launer et al. 1999; Ganguli et al. 2000; Kawas et al. 2000; Lobo et al. 2000; Chandra et al. 2001; Hendrie et al. 2001; Tang et al. 2001; Di Carlo et al. 2002; Edland et al. 2002; Knopman et al. 2002; Kukull et al. 2002; Fitzpatrick et al. 2004; Lopez-Pousa et al. 2004; Nitrini et al. 2004; Ravaglia et al. 2005a; Jellinger and Attems 2010).

Two factors contribute to the difficulty in establishing accurate incidence rates of AD: (1) determining the age at onset; and (2) defining a disease-free population. Nonetheless, studies illustrate the consistent increase in incidence rates with age from approximately 0.5% per year among individuals aged 65–70 to approximately 6–8% for individuals over age 85. The rapid rise in the frequency of AD with advancing age, combined with the relatively long duration of the illness, accounts in large part for the high prevalence of the disease worldwide. Improvement and standardization of diagnostic methods have provided a means to compare estimates of the frequency of AD across various populations.

ANTECEDENT RISK FACTORS THAT INCREASE THE RISK OF ALZHEIMER DISEASE

A large number of factors has been associated with increased risk of AD, but among those, cerebrovascular disease and it antecedents are the most consistently reported (Table 1). A history of diabetes, hypertension, smoking, obesity, and dyslipidemia have all been found to increase risk. Interestingly cerebrovascular disease, including large cortical infarcts, single strategically placed infarcts, multiple small infarcts, cerebral hemorrhage, cortical changes owing to hypoperfusion, white matter changes and vasculopathies, are all antecedents to dementia in general (Barba et al. 2000; de Koning et al. 2000; Desmond et al. 2000, 2002; Zhu et al. 2000; Henon et al. 2001; Klimkowicz et al. 2002; Honig et al. 2003; Liebetrau et al. 2003; Ivan et al. 2004; Linden et al. 2004; Srikanth et al. 2004; Tang et al. 2004; Zhou et al. 2004; de Koning et al. 2005; Kuller et al. 2005; Gamaldo et al. 2006; Jin et al. 2006; Simons et al. 2006; Srikanth et al. 2006; Yip et al. 2006; Jin et al. 2008; Reitz et al. 2008; Rastas et al. 2010).

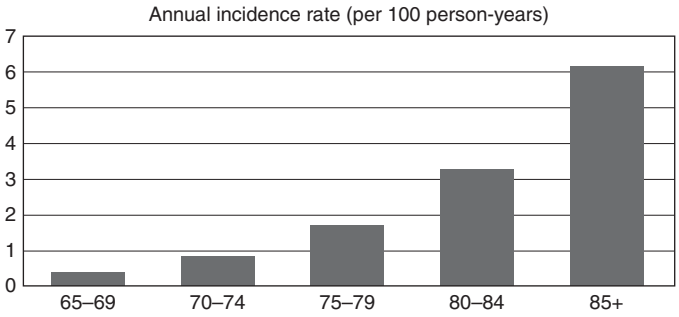

Figure 1. The annual incidence rate (per 100 person-years) for Alzheimer disease. This graph is an estimate of the data collected in 24 published studies.

Table 1. Factors that modify the risk of Alzheimer disease

Antecedent	Direction	Possible mechanisms
Cardiovascular disease	Increased	Parenchymal destruction Strategic location ↑ Aβ deposition
Smoking	Increased	Cerebrovascular effects Oxidative stress
Hypertension	Increased and decreased	Microvascular disease
Type II diabetes	Increased	Cerebrovascular effect Insulin and Aβ compete for clearance
Obesity	Increased	Increased risk of type II diabetes inflammatory
Traumatic head injury	Increased	↑Aβ and amyloid precursor protein deposition
Education	Decreased	Provides cognitive reserve
Leisure activity	Decreased	Improves lipid metabolism, mental stimulation
Mediterranean diet	Decreased	Antioxidant, anti-inflammatory
Physical activity	Decreased	Activates brain plasticity, promotes brain vascularization

Cerebrovascular Disease

While it is clear that cerebrovascular disease may present with manifestations resembling dementia, purely vascular dementia is uncommon. More often cerebrovascular disease co-exists with AD, so that evidence of both vascular disease and prototypical AD manifestations is present (Schneider and Bennett 2010). Pendlebury and Rothwell (2009) analyzed data from several hospital- and population-based cohorts (7511 patients) and estimated a frequency of new-onset dementia to be approximately 7% following a first stroke. Interestingly, the twofold increased risk of dementia after incident stroke was independent of the level or the rate of change of prestroke cognitive function, suggesting that prestroke cognitive function is not a major determinant of the effect of stroke on the risk of poststroke dementia (Reitz et al. 2008). The proposed mechanisms by which stroke could lead to cognitive impairment include destruction of brain parenchyma with atrophy (Fein et al. 2000; Jellinger 2002), damage in strategic locations that leads to amnestic syndromes, such as thalamic strokes, an increase in Aβ deposition and the combination of vascular and Alzheimer-type pathology (Blennow et al. 2006). As one possible mechanism for an increase in Aβ, there is evidence from rodent models of ischemia and hypoxia owing to hypoperfusion that a resulting overexpression of p25 and cdk5 increases levels of BACE1, which in turn increases amyloid precursor protein (APP) processing (Wen et al. 2007, 2008).

White matter hyperintensities are frequently observed by MRI in patients with dementia, but the mechanisms by which white matter changes contribute to cognitive decline are unclear. Moreover because hypertension, diabetes and microvasuclar disease are each associated with these changes, there is no clear process to explain the effect on cognition or their role in Alzheimer disease. Thalamic vascular disease can lead to lower performance on cognitive tasks, particularly those associated with frontal and temporal lobe function, including memory storage and retrieval (Swartz et al. 2008; Wright et al. 2008).

Hypertension

Cross-sectional and longitudinal studies implicate blood pressure as a possible contributor to late-life dementia. Observational studies of the association between elevated blood pressure during middle age and late-life cognitive impairment suggest that mid-life hypertension increases the risk of late-life dementia (Kilander et al. 2000; Launer et al. 2000; Wu et al. 2003; Yamada et al. 2003; Elias et al. 2004; Whitmer et al. 2005b). When hypertension is assessed in later life, the association is somewhat ambiguous, in that both high and abnormally low

blood pressure are associated with dementia (Skoog et al. 1996; Knopman et al. 2001; Morris et al. 2001; Ruitenberg et al. 2001; Tyas et al. 2001; Bohannon et al. 2002; Lindsay et al. 2002; Posner et al. 2002; Elias et al. 2003; Kuller et al. 2003; Piguet et al. 2003; Qiu et al. 2003; Reinprecht et al. 2003; Verghese et al. 2003a; Hebert et al. 2004; Solfrizzi et al. 2004; Tervo et al. 2004; Borenstein et al. 2005; Petitti et al. 2005; Waldstein et al. 2005). With Alzheimer disease onset and progression, blood pressure begins to decrease, possibly related to vessel stiffening, weight loss, and changes in the autonomic regulation of blood flow. Hypertension is a treatable medical disorder, but clinical trials of antihypertensive medications in AD patients have been attempted with inconsistent results (Forette et al. 2002; Lithell et al. 2003; Tzourio et al. 2003; Peters et al. 2010).

Type II Diabetes

The presence of type II diabetes is associated with a approximately twofold increased risk of AD (risk ratios vary between 1.5 and 4.0; Luchsinger et al. 2001; Peila et al. 2002; Farris et al. 2003; Luchsinger et al. 2004a). It has been suggested that diabetes directly affects Aβ accumulation in the brain because hyperinsulinemia, which accompanies type II diabetes, disrupts brain Aβ clearance by competing for the insulin-degrading enzyme (Selkoe 2000; Farris et al. 2003). Receptors for advanced glycation end-products, which also play a role in the pathogenesis of diabetes, are present in cels associated with senile plaques and neurofibrillary tangles have been shown to be one example of a cell surface receptor for Aβ. Excess adipose tissue may also predispose to type II diabetes by producing adipokines critical to metabolism and cytokines important in inflammation. Adiponectin, leptin, resistin, TNF-α and IL-6 are also produced and correlate with insulin resistance and hyperinsulinemia, which in turn may directly or indirectly affect AD risk (Trujillo and Scherer 2005; Yu and Ginsberg 2005). A meta-analysis of longitudinal studies examining type II diabetes and other disorders of glucose or insulin levels found a pooled effect size for diabetes of 1.54 in increasing AD risk (95% confidence interval, CI, 1.33–1.79; $z = 5.7$; $p < .001$; Profenno et al. 2009).

Reger et al. (2008) showed that the administration of intranasal insulin improved cognitive performance in the early phases of AD and in patients with amnestic mild cognitive impairment, as did a 6-month trial of the PPAR-γ agonist, rosiglitazone (Watson et al. 2005). Another study (Risner et al. 2006) in patients with AD lacking the APOE-ε4 allele showed significant although small improvements in cognitive and functional improvement in response to rosiglitazone, whereas in a study by Sato et al. (2009), treatment with 15–30 mg pioglitazone daily for 6 months led to improvements in cognitive function and regional cerebral blood flow in the parietal lobe.

Body Weight

Several cross-sectional and case–control studies found that low body mass index or being underweight were apparent risk factors for dementia and age-related brain changes such as atrophy (Faxen-Irving et al. 2005). In contrast several prospective studies linked both low and high body weight, weight loss and weight gain to risk of AD (Nourhashemi et al. 2002, 2003; Gustafson et al. 2003; Bagger et al. 2004; Brubacher et al. 2004; Buchman et al. 2005; Goble 2005; Jeong et al. 2005; Kivipelto et al. 2005; Razay and Vreugdenhil 2005; Rosengren et al. 2005; Stewart et al. 2005; Tabet 2005; Whitmer et al. 2005a; Waldstein and Katzel 2006; Arbus et al. 2008; Atti et al. 2008). The strongest effect was in a meta-analysis associating obesity (assessed by high body mass index) and the risk of AD (odds ratio, OR, 1.59 95% CI 1.02–2.5; $z = 2.0$; $p = .042$) (Profenno et al. 2009). The mechanisms by which body weight alters disease risk are unknown, but may include effects such as insulin resistance or the co-incidence of type II diabetes.

Smoking

Case–control studies initially suggested that smoking lowers the risk of Alzheimer disease, but subsequent prospective studies showed an

increased risk or no association (Doll et al. 2000). Smoking may increase the risk of dementia by augmentation of cholinergic metabolism, that is, up-regulating cholinergic nicotinic receptors in the brain (Whitehouse et al. 1988). Cholinergic deficits, characterized by reduced levels of acetylcholine, choline acetyl transferase and/or nicotinic acetyl choline receptors, are invariably found in AD brains. However, nicotine itself increases acetylcholine release, elevates the number of nicotinic receptors, and improves attention and information processing. These actions may be opposed by elevated oxidative stress caused by smoking, and oxidative stress has been implicated as a putative AD mechanism (Rottkamp et al. 2000; Perry et al. 2002) through the generation of free radicals and affecting inflammatory–immune systems, which in turn can activate phagocytes that generate further oxidative damage (Traber et al. 2000).

Traumatic Brain Injury

Compared with those without a history of trauma, individuals having suffered traumatic brain injury have a higher risk of dementia, particularly those who carry the APOE-ε4 allele (Koponen et al. 2004). A meta-analyses demonstrated that the risk of dementia is higher among men (but not women) with a history of traumatic brain injury (Fleminger et al. 2003). Postmortem and experimental studies do support a link: After human brain injury, both Aβ deposition (Hartman et al. 2002; Iwata et al. 2002; Stone et al. 2002) and intraneuronal tau pathology are increased, even in younger patients (Smith et al. 2003). In addition, CSF Aβ levels are elevated and APP is overproduced (Emmerling et al. 2000; Franz et al. 2003).

PROTECTIVE FACTORS THAT REDUCE RISK OF ALZHEIMER DISEASE

Cognitive Reserve

Individuals with intellectually enriched lifestyles, such as those with high educational and/or occupational attainment, have a reduced risk of expressing AD pathology clinically. While several studies reported no association between educational level and risk of AD (Hall et al. 2000; Chandra et al. 2001), a lower risk of dementia in general in subjects with higher education has been reported by several others worldwide (Evans et al. 1993, 1997; Letenneur et al. 1994, 1999; Stern et al. 1994; White et al. 1994; Qiu et al. 2001).

There is also evidence for a role of education in age-related cognitive decline, with several studies of "normal aging" reporting slower cognitive and functional decline in individuals with higher educational attainment (Chodosh et al. 2002). These studies suggest that the same education-related factors that delay the onset of AD-type dementia also allow individuals to cope more effectively with brain changes encountered in normal aging. In an ethnically diverse cohort of nondemented elders in New York City, increased literacy was also associated with slower decline in memory, executive function, and language skills (Manly et al. 2005).

Numerous studies have also explored the relationship between leisure activities and incident dementia. Community activities and gardening were also protective for incident dementia in China (Zhang et al. 1999). Having an extensive social network was protective for the development of dementia (Fratiglioni et al. 2004), and engagement in mental, social, and other productive activities was associated with decreased risk of incident dementia (Wang et al. 2002). Participation in a variety of leisure activities characterized as intellectual (e.g., reading, playing games, going to classes) or social engagements (e.g., visiting friends or relatives) was assessed in another population study of nondemented elderly in New York (Scarmeas et al. 2001). During follow-up, subjects with high leisure activity had 38% less risk of developing dementia. In another prospective study, frequency of participation in common cognitive activities (i.e., reading a newspaper, magazine, or book) was assessed at baseline for 801 elderly Catholic nuns, priests and brothers without dementia (Wilson et al. 2002a). Finally, in another prospective cohort from New York,

participation in leisure activities, particularly reading, playing board games or musical instruments, and dancing, was associated with a reduced risk of incident dementia (Verghese et al. 2003b). Increased participation in cognitive activities was also associated with reduced rates of memory decline in this study.

A meta-analysis examined cohort studies of the effects of education, occupation, premorbid IQ and mental activities on dementia risk (Valenzuela and Sachdev 2005). A summary analysis was based on an integrated total of 29,279 individuals from 22 studies. The median follow-up was 7.1 years. The summary odds ratio for incident dementia for individuals with high brain reserve compared with low brain reserve was 0.54 (95% CI 0.49–0.59, $p < 0.0001$), that is, a decreased risk of 46%. Eight out of 33 data sets showed no significant effect, whereas 25 out of 33 demonstrated a significant protective effect. The authors found a significant negative association between incident dementia risk (based on differential education) and the overall dementia rate for each cohort ($r = -0.57$, $p = 0.04$), indicating that in negative studies there was a lower overall risk of incident dementia in the cohort.

In contrast to the studies above, in which greater cognitive reserve was associated with better outcomes, a series of studies of patients with AD suggested that those with higher reserve have poorer outcomes (Table 1). In prospective studies of AD subjects matched for clinical severity at baseline (Geerlings et al. 1999; Stern et al. 1999), patients with greater education or occupational attainment died sooner than those with less attainment. Similarly, higher educational or occupational attainment (Stern et al. 1999; Scarmeas et al. 2006a), increased engagement in leisure activities (Helzner et al. 2007), and greater lifetime cognitive activity (Wilson et al. 2010) have each been associated with more rapid cognitive decline in patients with diagnosed AD. Although at first these findings appear contraintuitive, they are consistent with the cognitive reserve hypothesis. The hypothesis predicts that, at any level of assessed clinical severity, the underlying pathology of Alzheimer disease is more advanced in patients with higher than those with less cognitive reserve. This would result in the clinical disease emerging when pathology was more advanced, as suggested by the incidence studies reviewed above. This disparity in degree of pathology would be present at more advanced clinical stages of the disease as well. At some point the greater degree of pathology in the high-reserve patients would result in more rapid death. Higher educational attainment and greater engagement in leisure activities and lifetime cognitive activities have also been associated with more rapid cognitive decline in patients with Alzheimer disease.

Diet

Dietary fats can increase cholesterol levels, which in turn can increase vascular risk in the brain. This sequence may also increase the risk of AD (Sparks et al. 2000). Intake of saturated fats in the fifth (highest) quintile compared with the first quintile of dietary fats was associated with a doubling of risk of incident Alzheimer disease. Trans-unsaturated fats were associated with a 3-times-higher risk of developing AD, whereas the highest intake of n-6 polyunsaturated fats and monounsaturated fat reduced AD risk (Morris et al. 2003). An increased risk of AD has also been associated with higher intake of total and saturated fat, with no evidence of an association with polyunsaturated fat (Luchsinger et al. 2002).

Omega-3 fatty acids stems are essential dietary components in early brain development. Many studies have found that consumption of fish or omega-3 fatty acids is associated with a reduced risk of AD (Morris et al. 2003; Schaefer et al. 2006; van Gelder et al. 2007). For example, a study in France found that weekly consumption of fish was associated with reduced AD risk, and regular consumption of omega-3 rich oils was associated with increased risk of all causes of dementia (Barberger-Gateau et al. 2007).

Two studies found a lower risk of Alzheimer disease in individuals with a higher dietary intake of vitamin D (Engelhart et al. 2002; Morris et al. 2002). This association was not

noted in a third study, perhaps because the level of vitamin D intake was lower (Luchsinger et al. 2003).

Total homocysteine has also been inconsistently associated with AD (Luchsinger et al. 2004b; Seshadri 2006; Reitz et al. 2009). Concentrations of homocysteine are largely determined by certain B vitamins. Based on folate levels measured in serum, there was preliminary evidence from two studies that low folate levels are associated with increased AD risk (Wang et al. 2001; Ravaglia et al. 2005b). Some studies that used estimated dietary intake of folate and B vitamins based on self-reported information reported conflicting results. One reported an association between higher intake of folate and reduced risk of AD (Luchsinger et al. 2007), whereas another did not find a significant reduction in AD risk associated with folate intake (Morris et al. 2006). Neither study found an association between vitamins B6 or B12 and risk of AD.

Inconsistencies in the existing literature regarding some of the above dietary elements and AD risk may be a result of failure to consider possible additive and interactive (antagonistic or synergistic) effects among nutritional components, which may be better captured in a composite dietary pattern such as the Mediterranean diet. The latter is characterized by high intake of vegetables, legumes, fruits, and cereals; high intake of unsaturated fatty acids (mostly in the form of olive oil), but low intake of saturated fatty acids; a moderately high intake of fish; a low-to-moderate intake of dairy products (mostly cheese or yogurt); a low intake of meat and poultry; and regular but moderate amounts of ethanol, primarily in the form of wine and generally during meals (Trichopoulou et al. 2003). In one study (Scarmeas et al. 2006b), higher adherence to the Mediterranean diet was associated with lower risk of AD (hazard ratio, 0.91; 95% CI, 0.83–0.98; $p = 0.015$). Compared with subjects in the lowest Mediterranean diet tertile, subjects in the middle tertile had an AD hazard ratio of 0.85 (95% CI, 0.63–1.16) and those in the highest tertile had a hazard ratio of 0.60 (95% CI, 0.42–0.87) (p for trend = 0.007). In a follow-up analysis, the Mediterranean diet was also associated with a reduced risk of developing mild cognitive impairment and of progression from mild cognitive impairment to AD (Scarmeas et al. 2009).

Physical Activity

Exercise can enhance learning in both young and aged animals (van Praag et al. 1999), activate brain plasticity mechanisms, remodel neuronal circuitry in the brain (Cotman and Berchtold 2002), promote brain vascularization (Black et al. 1990), and stimulate neurogenesis (van Praag et al. 1999). It may also increase neuronal survival and resistance to brain insults (Carro et al. 2001), increase levels of brain-derived neurotrophic factor, mobilize gene expression profiles that would be predicted to benefit brain plasticity (Cotman and Berchtold 2002), and reduce levels of C-reactive protein and interleukin-6, two inflammatory markers (Ford 2002; Reuben et al. 2003). A Cochrane review (Angevaren et al. 2008) found that eight of 11 random, controlled trials of exercise in older people without known cognitive impairment reported that aerobic exercise interventions were associated with improvements in cognitive function.

Although some studies have failed to detect an association between physical activity and dementia (Wang et al. 2002; Wilson et al. 2002a; Verghese et al. 2003b), others have observed a beneficial role (Podewils et al. 2005; Rovio et al. 2005; Larson et al. 2006; Wang et al. 2006). A study of 1880 community-dwelling elders without dementia living in New York City investigated the combined association of diet and physical activity with Alzheimer risk. A combination of adherence to a strict Mediterranean-type diet and regular physical activity (compared with no or minimal physical activity) was associated with a significant reduction in risk of AD.

Cognitive Enhancement

Several studies have specifically examined the potential effects of cognitive engagement on the risk of AD (Wilson et al. 2002b, 2007;

Verghese et al. 2003b; Akbaraly et al. 2009). The studies used self-report of the frequency of involvement in specific activities that potentially have a cognitive component. In the Three-City cohort study, analyses were carried out on 5698 dementia-free participants aged 65 and over. Stimulating leisure activities were significantly associated with a reduced risk of AD (hazard ratio (HR) = 0.39). This finding was independent of other proxies of cognitive reserve and remained significant after adjusting for vascular risk factors, depressive symptoms and physical functioning.

GENETIC EPIDEMIOLOGY

Rare Variants

Rare mutations in three genes have been firmly implicated in familial early-onset disease: *APP*, *PSEN1*, and *PSEN2* (Table 2; Goate et al. 1991; Levy-Lahad et al. 1995a,b; Rogaev et al. 1995; Sherrington et al. 1995, 1996). These mutations have high penetrance, are mostly inherited in an autosomal dominant pattern and lead with certainty to enhanced relative levels of the Aβ42 peptide, its aggregation and an early onset of disease, typically beginning in the fourth or fifth decade of life. *APP* mutations account for an even smaller fraction (less than 1% of all AD patients). Rare variants such as these are occasionally seen in families of patients with familial Alzheimer disease having later onset (Athan et al. 2001). All *APP* missense mutations influence APP proteolytic processing and/or aggregation, because they are positioned in or near the Aβ-coding exons (16 and 17) of APP (see AD Mutation Database, http://www.molgen.vib-ua.be/ADMutations/). The mutation spectrum also includes microduplication at the *APP* locus on Ch 21. At the time of writing, 182 different AD-related mutations in 401 families have been identified in *PSEN1*, whereas only 14 mutations in 23 families were detected in *PSEN2* (http://www.molgen.vib-ua.be/ADMutations/). The majority of *PSEN* mutations are single-nucleotide substitutions, but small deletions and insertions have also been described. *PSEN* mutations alter the γ-secretase-mediated proteolytic cleavage of *APP*, resulting in an increased $A\beta_{42}/A\beta_{40}$ ratio by an increase in $A\beta_{42}$ and/or a decrease in $A\beta_{40}$, suggesting a partial loss-of-function mechanism rather than a gain-of-function in *PSEN* (see Tanzi 2011 for a detailed review). Although mutations in these three genes represent rare causes of AD, their discovery greatly supported a pivotal role for Aβ in the pathogenesis of AD. According to this amyloid (or Aβ hypothesis), neurodegenerative processes are the consequence of an imbalance between Aβ production and Aβ clearance, suggesting

Table 2. Gene variants associated with Alzheimer disease

Gene	Main alteration	Presumed mechanism
Amyloid precursor protein (*APP*)	Mutation	Autosomal dominant, mostly early onset
Presenilin 1 (*PSEN1*)	Mutation	Autosomal dominant, mostly early onset
Presenilin 2 (*PSEN2*)	Mutation	Autosomal dominant, mostly early onset
Apolipoprotein-E (*APOE*)	Common variant	Familial and sporadic, late onset
Sortilin-related receptor, L(DLR class) A repeats-containing (*SORL1*)	Common variant	Familial and sporadic, late onset
Clusterin (*CLU*)	Common variant	Sporadic, late onset
Phosphatidylinositol binding clathrin assembly protein (*PICALM*)	Common variant	Sporadic, late onset
Complement component (3b/4b) receptor 1 (*CR1*)	Common variant	Sporadic, late onset
Bridging integrator 1 (*BIN1*)	Common variant	Sporadic, late onset

that other genes involved in these pathways might also turn out to be risk factors.

Common Variants

The strongest common genetic variant for typical late-onset AD beginning after age approximately 65 years is apolipoprotein E (*APOE*), a three-allele polymorphism (ε2, ε3, and ε4) where ε3 is considered a neutral allele, ε4 the high-risk allele, and ε2 a protective allele (Table 2). The ε4 allele influences age at onset in a dose-dependent manner (Corder et al. 1993). However, more than half of the patients with late-onset disease do not have the high-risk ε4 allele. The population attributable risk related to APOE-ε4 has been estimated at 20% (Slooter et al. 1998). Genome-wide association (GWA) studies have identified variants in *CLU*, *PICALM*, *CR1*, and *BIN1* as putative susceptibility loci (Harold et al. 2009; Lambert et al. 2009; Seshadri et al. 2010). These genetic variants have been confirmed in other non-Hispanic and Hispanic populations (Carrasquillo et al. 2010; Jun et al. 2010; Lee et al. 2010). The odds ratios for these genes are much lower than for *APOE* (OR = are 3.2 and 14.9 for ε3/ε4 and ε4/ε4, respectively [Farrer et al. 1997]) and range from 1.16 to 1.20 for *CR1*, *CLU*, and *PICALM*.

Familial Late-Onset Alzheimer Disease

Bertram et al. (2008) performed a GWA study in 1376 samples from 410 families with late-onset Alzheimer disease (LOAD) and subsequently replicated their findings. A locus on chromosome 14q31 was strongly associated with LOAD, but the identity of the underlying locus is unknown and may be a modifier of onset age. The results of GWA studies in the NIA-LOAD Family Study, involving 900+ families stratified by APOE genotype, also identified single-nucleotide polymorphisms on chromosome 10p14 in *CUGBP2* with genome wide significance within individuals with one *APOE* ε4 allele, which was replicated in an independent Caribbean Hispanic cohort (Wijsman et al. 2011). The NIA-LOAD Family Study also replicated the variants in *BIN1* and provided modest confirmation for *CLU*, but not for *CR1* or *PICALM* after *APOE* adjustment (Hollingworth et al. 2011; Naj et al. 2011). The role of these genes in the pathogenesis of Alzheimer's disease remains to be determined, but it is clear that large sample sizes have enabled identification of these putative gene variants.

Finally, variants in *SORL1*, which encodes a protein involved in trafficking of APP, are associated with late-onset AD. Although in line with other recently described genetic links for AD (Lee et al. 2007; Rogaeva et al. 2007), the effect sizes of the *SORL1* associations are modest (Reitz et al. 2011). Variants in the SORL1 homolog, SORCS1, are also modestly associated with AD. Overexpression of either gene leads to a decrease in Aβ levels in cultured cells, whereas inhibition by RNAi increases Aβ. Thus, both genes may play a role in AD pathogenesis.

Although these results of the published GWA studies are informative, the genetic associations need functional validation. GWA studies represent a method of screening the genome, but limitations exist in their ability to detect true associations. The results of such studies might be difficult to replicate if the real effect turns out to be smaller than the effect observed in the initial study. In addition, GWA studies may not detect associations with multiple rare variants at a single site (which are better detected by linkage studies) or with single rare variants (minor allele frequency $<5\%$). Finally, such studies alone cannot prove causality or establish the biological significance of an observed genetic association.

CONCLUSIONS

Our understanding of AD pathogenesis has grown substantially over the past two decades. However, with the large numbers of individuals reaching the age of highest risk, some would say that we have a long way to go toward preventing or limiting the full impact of the disease. Current treatments are palliative at best and newer therapies remain unproven. Knowing who is a risk and why will make prevention and

management easier in the future (Aisen et al. 2011; Lee et al. 2011; Schenk et al. 2011).

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