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Children of Persons With Alzheimer Disease:

What Does the Future Hold?

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Abstract

Children of persons with Alzheimer disease (AD), as a group, face an increased risk of developing AD. Many of them, throughout their adult lives, seek input on how to reduce their chances of one day suffering their parent's fate. We examine the state of knowledge with respect to risk and protective factors for AD and recommend a research agenda with special emphasis on AD offspring.

Keywords

Alzheimer disease offspring; risk factors

Much has been learned about Alzheimer disease (AD) since Alois Alzheimer first described it more than a century ago,[1] but to date no consensus has been reached on its etiology, no universally accepted preventive interventions have become available, and treatments are only minimally effective. Although a considerable amount of research is underway, much of it is as yet inconclusive and often mired in significant methodologic challenges. Meanwhile, the number of persons afflicted with AD has been steadily increasing. For the United States alone, estimates have been as high as 5 million in 2007,[2] up from 4 million.[3] Others, using different diagnostic criteria, estimated the prevalence of AD at 1.9 million.[4,5] The most recent report, the Aging Demographic and Memory Study (ADAMS),[6] a supplemental study of the Health and Retirement Study, yielded an estimate of 2.5 million individuals with AD at the age of 60 years and older in the United States in 2002. ADAMS was based on a nationally representative population sample with in-person assessments of 856 individuals between 2001 and 2003. It is the first study to assess individuals from all regions of the United States to estimate prevalence of dementia and, therefore, should account for regional and ethnic differences in prevalence. Whatever their precise numbers, AD patients are expected to increase as the estimated 70 to 80 million baby boomers (with their advancing age and increasingly greater longevity compared with prior more vulnerable to manifesting the disease. For example, by 2050, the number of people with AD in the United States may range from 11 to 16 million.[2]

Concerning global prevalence, the best estimates available suggest that 24 to 27 million individuals currently have AD and this number is projected to rise to more than 100 million by 2050.[7,8] However, the rate of increase over that interval is not expected to be uniform. Differences in life expectancy across regions of the world, differences in survival after diagnosis of dementia, varying diagnostic conventions, and difficulties in ascertainment (especially in residents of rural underdeveloped areas) and differential exposure to risk factors may play a role (eg, low levels of cardiovascular risk found in some developing countries). Some investigators concluded that incidence and prevalence of dementia show relatively little geographical variation once methodologic issues are taken into account, although there may be greater inconsistencies in some types of dementia (eg, AD) than in others.[9] Much more information than currently available is clearly needed.

In light of the increasing magnitude of the suffering caused by AD, and considering its economic burden (in the United States more than $148 billion/y in 2007[2]), the search for factors that might increase or lower the risk of manifesting the disease takes on crucial importance. Observational studies have already suggested several factors that might trigger, induce, or accelerate the development of AD; yet, only a few are generally accepted.[10,11] Although it may take many years before efforts to prevent or successfully treat AD will come to fruition, even delaying its onset could substantially reduce prevalence and cost.[12,13]

Further research may be of particular urgency for the population of adult children of persons with AD ("AD offspring") as they themselves advance in age. There are, however, surprisingly few data available on the risks faced specifically by AD offspring.[14] Even their overall number, which most likely ranges well into millions, remains as yet unknown. Longitudinal studies ongoing worldwide are expected to yield much needed information. In the United States, for example, studies focusing on AD offspring include, but are not limited to, the Risk Evaluation and Education for Alzheimer's Disease (REVEAL) study,[15] the Wisconsin Registry for Alzheimer Prevention (WRAP) study,[16] the Washington University Adult Children study,[12] and the Framingham Offspring study.[17] Results of these investigations will complement what has been learned from longitudinal studies of mixed samples of AD relatives (children and siblings or parents), including the National Institute of Mental Health's Biomarkers in Older Controls At Risk for Dementia (BIOCARD) study,[18] studies of persons at risk for AD,[19–26] additional family studies of AD,[27–31] and twin studies.[32]

In this article, we will (i) briefly summarize generally accepted information regarding risk and protective factors and (ii) make recommendations for a research agenda designed to assess genetic and nongenetic risks and protective factors with special emphasis on AD offspring. Our purpose is not to supply a comprehensive review of the literature, but to provide enough background to understand the urgent need for further research in AD and the recommendation of strategies for future research.

RISK FACTORS FOR AD

Risk factors for AD are notoriously difficult to isolate as they interact with each other in a variety of ways. As a result, the outcomes of different studies are sometimes hard to reconcile and frequently require further clarification. Moreover, there is no uniform method of reporting (eg, prevalence, incidence, and lifetime risk), further complicating comparison of study outcomes. Nevertheless, 2 risk factors have become firmly established: chronologic age and positive family history.

Chronologic age has emerged as a crucially important risk factor, not only in itself but also, as we will see, through its interactions with a variety of other risk factors. For example, in a recent collaborative study carried out in 8 European countries, the pooled AD incidence rate per 1000 person-years rose from 1.2 to 9.1 and 35.3 for ages 65 to 69, 75 to 79, and 85 to 89 years, respectively.[33] In the United States, the current prevalence of AD is estimated as 2%, 19%, and 42% for age groups 65 to 74, 75 to 84, and 85+ years, respectively.[2]

Positive family history of AD is another risk factor for AD, independent of any identified genetic factors. It is generally reported that a person with at least 1 first-degree relative with dementia has 2 to 4 times the lifetime risk of developing AD compared with someone without such a relative.[28] These estimates may be sensitive to age structure and other modeling issues, such as the uncertainty of the diagnosis of AD/dementia in long-deceased relatives, and conversely, the inability to classify relatives who did not live through the age of risk as clearly free of AD/dementia. Moreover, although positive family history increases the risk for developing AD, this effect may diminish with age and may be minimal or absent after the age of 85 years.[31] Other studies point to a different interaction effect of chronologic age and positive family history. The age at which the first-degree relative with AD (proband) manifests the symptoms of AD [age at onset (AAO)] may itself be a risk factor for the development of AD. The younger the proband's AAO, the greater the genetic risk for the relatives, regardless of the age of the relatives themselves.[34,35]

Within the group of first-degree relatives, the highest risk is faced by persons who have an identical twin with AD. The study of twins (identical or monozygotic and fraternal or

dizygotic) offers a unique opportunity to explore the relative contributions of genetic and other influences to the risk of developing AD. In the largest twin study to date, the Swedish twin study,[32] heritability of AD was estimated to be 58%, with nongenetic risk factors playing an important role (nonshared environmental influences 23%, shared environmental influences 19%). In addition, twin studies clearly document that even in concordant twins (ie, both twins develop AD) there can be differences in AAO of as much as 16 years, indicating that the effects of both chronologic age and positive family history vary significantly as they interact with other risk factors.

Genetic Risk Factors

AD provides one of the best examples of the importance of distinguishing between 2 types of genetic variants that contribute to the risk of developing a disease: (i) Highly penetrant variants are usually rare, inherited in a simple (Mendelian) pattern, and provide remarkable insight into the basic biologic process underlying the disease. (ii) Less penetrant variants display complex segregation patterns and, therefore, may be less informative than Mendelian variants with respect to elucidation of pathobiology. However, they are often common, which increases the likelihood that they will substantially enhance our understanding of disease risk at the population level.[36] More than 100 genes have been implicated in the development of AD through genetic association studies (see AlzGene, www.alzgene.org[37]) and other studies,[38–43] but only 4 genes have so far been clearly established as contributing to the development of the disease: the 3 so-called "Alzheimer genes" [Amyloid Precursor Protein (*APP*), *Presenilin 1 (PS1)*, and *Presenilin 2 (PS2)*] and the susceptibility gene APOEe4. The 3 Alzheimer genes all display rare but highly penetrant autosomal dominant mutations that lead to early-onset AD. In the 1980s, the study of the Alzheimer plaques, consisting largely of β-amyloid protein (Aβ), focused interest on Aβ[44] and led to the discovery that alterations in *APP* on chromosome 21 are a cause of some cases of familial AD.[45] *PS1*[46] and *PS2*[47] were subsequently discovered by linkage to other families with AD. The pathogenic mutations in all 3 of these genes were found to have the common effect of causing aberrant processing of APP to produce elevated levels of $A\beta_{42}$,[48] the more fibrillogenic form of Aβ thought to be the most critical in causing the amyloid pathology. Further evidence for this "amyloid hypothesis" came from the study of Down syndrome with essentially all persons living into their sixth decade of life developing AD neuropathology and some progressive cognitive and behavioral deterioration.[49] The amyloid hypothesis unifies a number of diverse observations, contributes substantially to our understanding of the pathobiology of AD,[21,50,51] and has opened up promising therapeutic avenues even though overproduction of $A\beta_{42}$ does not by itself explain all aspects of AD pathology.[52] However, the Alzheimer genes are so rare that all 3 account for <1% of AD.[51]

By contrast, the ε4 allele of the gene encoding apolipoprotein E (*APOE* ε4) has been established as the most important genetic risk variant in population samples of all ages. *APOE* ε4 is common but only modestly penetrant, and it remains unclear at a biologic level as to how it contributes to the development of AD. Diverse animal experiments have suggested that the risk of *APOE* ε4 for AD may be mediated through either amyloid-dependent[53] or amyloid-independent[54] pathways. We expect that multiple additional AD susceptibility genes (most likely relatively low penetrance variants) and nongenetic risk factors will be discovered that contribute to AD risk. Fortunately, the technology is now available to identify such variants through well-powered genome-wide association (GWA) studies. The International HapMap Project[55] has identified several million single nucleotide polymorphisms (SNPs) that can be used (employing currently available commercial assays) to conduct GWA studies in samples drawn from diverse ethnic populations. Some GWA studies of AD are now underway. The cost is relatively low even for samples of several thousand individuals.

APOE ε4, the only confirmed susceptibility gene for AD, has been found in over 100 studies to increase vulnerability to AD at all ages. In the United States, about one-half to two-thirds of persons with late-onset AD carry the *APOE* ε4 allele.[56–58] The frequency varies with age and findings vary as to the magnitude of risk conferred by APOE status.[59] A recent analysis of European Americans[60] determined that ε4 homozygotes occurred significantly more often among individuals with early-onset AD (20.3%) than among late-onset AD (8.2%) confirming the findings from previous studies. It has been known for a decade[61] that the *APOE* ε4 effect is evident at all ages between 40 and 90 years, but diminishes after the age of 70 years. For heterozygous *APOE* ε4 carriers, compared with noncarriers, the increased lifetime risk of developing AD has been estimated as 3-fold to 4-fold, and for homozygotes as 2-fold to 10-fold or 15-fold. In population studies, the percentage of persons with AD carrying 1 or 2 *APOE* ε4 alleles ranges from approximately 50% to 70%.[56] Risk estimates for dementia in the general population range from 25% to 50%, and studies of *APOE* ε4 homozygotes found a dementia prevalence of 50%[62] or less.[57,61]

Global variation in *APOE* ε4 allelic frequency could contribute to different rates of AD among populations with European, Asian, and African ancestry. In European populations, prevalence estimates for the *APOE* ε4 allele range from 7.3% (Poles) to 19.8% (Norwegian); the range is somewhat more restricted in Asia/East Asia, extending from 0.0% (Koch) to 17.0% (Javanese), and wider in Africa, where prevalence estimates range from 3.0% (Senegal) to 40.7% (Biaka). Allele frequencies are available at http://alfred.med.yale.edu. An extensive review of ethnic differences[63] concludes that despite differences in sampling methods, definitions of dementia, and definitions of race/ethnicity as well as discrepancies in functional and neuropsychologic assessments, there are ethnic differences in the observed prevalence and incidence of cognitive impairment, dementia, and AD. Although AD has been found in all ethnic groups that have been examined, data are relatively scarce, and arguably might be more indicative of the challenges of culturally fair measurement than of decreased cognitive functioning in the test subjects.[64–66] For example, despite its relatively low frequency in China (8.1%), the *APOE* ε4 allele remains an important risk factor for AD.[67] Indeed, according to more recent epidemiologic studies, the rate of AD in China may be similar to that in western populations.[68] It is possible also that *APOE* ε4 may not function as a risk factor across all populations such as in Chinese of Guangzhou[69] and Nigerians of Ibadan.[70] In African Americans too, several studies show little to no increase in the risk of AD with the *APOE* ε4 allele,[61,71–73] whereas others did find an association between *APOE* ε4 and AD.[74–76] The Wadi-Ara Arabs in northern Israel constitute another population of interest, given their unusually low ε4 allele frequency despite high rates of AD.[77] According to 1 report,[78] lower serum cholesterol was related to reduced risk of AD only in those who carried no ε4 alleles. Overall, the global data currently available do not support definitive conclusions regarding *APOE* ε4 and AD (small sample sizes and widely differing methods across studies may be among the most important reasons). Nonetheless, *APOE* has been considered a good "anthropogenetic and clinical diagnostic marker."[79]

It is important to remain aware of the fact that not all carriers of the ε4 allele develop AD, even if they live to advanced old age, and many without ε4 do manifest the disease.[57,61,62,80–83] A variety of interacting risk and protective factors (as discussed below) has been implicated, but the mechanisms of these interactions are as yet to be explored. Meanwhile, the value of *APOE* in the diagnosis of AD remains to be established. *APOE* status has explicitly *not* been recommended for prediction by multiple national panels[84] (see http://www.acmg.net/resources.policies/pol-001.asp for the American College of Medical Genetics consensus statement recommending against routine genotyping of *APOE*).

Prominent among ongoing research exploring *APOE*-related issues is the multicenter REVEAL study,[15] aimed at understanding the impact of *APOE* testing. Careful estimates of the relation between *APOE*, positive family history, and disease risk, prepared for this study[85] suggest that the risk was highest for persons with 1 or more *APOE* ε4 alleles and a first-degree relative with AD. As mentioned earlier, however, the effect of positive family history varies with age until a maximum age after which it may no longer make a significant difference. *APOE* status may interact with chronologic age in a similar pattern: A recent update on dementia[51] confirmed earlier reports[61,86] that the *APOE* ε4 effect is strongest before the age of 75 years. Among findings supporting this conclusion are those of the Cache County study,[87,88] which indicate that the age-specific prevalence of AD reaches a maximum and then declines. The maximum was reached at the average ages of 73 and 87 years in *APOE* ε4 homozygotes and heterozygotes, respectively, whereas the comparable age in participants without ε4 alleles was 95 years. It has, therefore, been suggested that the strongest influence of *APOE* ε4 may be in accelerating the AAO of AD, and thereby, also lowering the age of maximum risk.[87]

In a similar vein, it has been proposed that *APOE* ε4 may be an indicator of a general frailty factor that may lead to death before the AAO of AD.[89,90] At the same time, this general frailty factor may increase vulnerability to AD in those who live long enough to manifest the disease. *APOE* ε4 has also been implicated in the excess mortality associated with AD, but again, the mechanisms behind this risk have as yet not been identified.[91] Methodologic issues have hampered research in this area and further investigations will require sophisticated methodology such as multistage survival models.

APP, PS1, PS2, and *APOE* ε4 overall account but for a small amount of the genetic component of the risk of AD. Additional unidentified genes are clearly in operation. As mentioned before, over 100 genes have already been implicated but have not as yet been confirmed. One recent example is the proposed linkage of AD risk to variants in the intronic region of the *SORL1* neuronal sorting receptor.[92] These variants may regulate the expression of *SORL1* that is involved in directing the intracellular trafficking of APP. Differences in *SORL1* expression levels could lead to quantitative differences in the pathways through which APP is processed. A second example comes from a recent genome-wide survey reporting that polymorphisms in the gene encoding for growth factor receptor-bound–associated binding protein-2 (GAB2) were associated with an increased risk of AD among persons carrying the *APOE* ε4 allele.[93]

Other Risk Factors

In addition to age, positive family history, the 3 Alzheimer genes, and *APOE* ε4, other potential risk factors such as head trauma, cardiovascular disease, hypertension, diabetes, and atherosclerosis have been suggested.[12] Sex (even after accounting for survival differences) may interact with *APOE* ε4 to influence cognitive decline[57,88,94] and, so may educational attainment and brain reserve.[95,96] The association between smoking and the development of dementia is unclear. Although animal experiments generally show a detrimental effect,[97] results of epidemiologic studies have varied, the more recent ones tending to show an increased risk for dementia in long-term smokers.[98]

There has also been support from epidemiologic studies for the protective effect of nutrition and dietary supplements.[99,100] Reportedly, certain fish,[101] n-3 fatty acids,[101] antioxidant supplements,[102–104] homocysteine, [105] and reduction of intake of saturated and trans-unsaturated fat[106] may provide protection against AD. There is some evidence that these dietary factors may interact with the *APOE* ε4 allele, but not in a consistent fashion.[107] In addition to, and possibly interacting with diet, exercise has been suggested as a potential protective factor. An emerging body of literature supports that suggestion, concluding that

physical exercise may protect against dementia.[108] Some of the positive effects of exercise likely reflect its effect on preserving cardiovascular health. Additionally, exercise has been shown to lead to increases in brain-derived neurotrophic factor (BDNF) that would promote brain plasticity.[109]

Other research has suggested that cognitively stimulating activity in mid-life and late-life may delay or prevent AD.[110–112] Finally, there is some evidence that occupations with higher cognitive demands may protect against manifestation of AD.[113,114] Notably, studies of leisure activities and occupation are observational and can suffer from reverse causation and third-variable problems that cannot be entirely answered by adding covariates to the analyses. Nonetheless, nutrition and daily activities are to a certain extent under an individual's control. In this sense, they are potentially modifiable by the individual and thus have appeal as targets for interventions.

Depression has long been associated with AD (as a precursor, prodrome, and symptom); yet, the links between them remain to be clarified. Nearly a decade ago, a relationship was reported between insulin levels and severity of AD and *APOE* genotype,[115] and more recently, a hypothesis proposed that insulin resistance (IR) may link AD and depression.[116] Epidemiologic evidence supports an association between insulin dysregulation, cognitive decline, and AD.[117] Although the exact mechanism of action of IR in the central nervous system is not known, it is thought that IR may lead to inadequate brain glucose metabolism. Glucose dysregulation clearly seems to increase the risk of AD even after exclusion of cardiovascular risk factors[118]; moreover, an association between IR-related vascular disorders and AD has been documented.[119] It has also been pointed out that IR may develop as a consequence of weight gain and obesity associated with the neurovegetative symptoms of depression and some of the common pharmacologic treatments for depressive disorders such as use of atypical antipsychotics and anticonvulsants.[120]

Diabetes has been reported to increase risk for cognitive decline and AD.[117,121–126] Potential mechanisms for an association between diabetes and AD are (a) through cerebrovascular disease,[127] (b) through increased oxidative stress,[128] (c) through generation of advanced glycosylated end products,[129] and (d) through insulin.[130] The Washington Heights/Hamilton Heights/Inwood Columbia Aging Project (WHICAP)[131] and Rotterdam[124] studies reported an increased association between diabetes and AD in subjects treated with insulin and a large proportion of diabetes in the elderly may be explained by IR.[128]

In addition to the likelihood that the IR-depression–AD association will help to identify biologic mechanisms in the development of AD, it has potential clinical usefulness. Early identification of a subgroup of patients with depressive disorders and IR, with or without additional risk factors for AD, could lead to appropriate changes in medication regimens, preventive measures targeting AD, earlier diagnosis, and intervention.

Observational data have suggested an association between hyperlipidemia and AD,[132,133] and also an association between use of lipid-lowering medications,[134] and a decreased risk of AD. In an observational study of 1037 postmenopausal women with coronary heart disease enrolled in the Heart and Estrogen/Progestin Replacement Study, women in the highest low-density lipoprotein (LDL) cholesterol quartile at cognitive testing had low Modified Mini-Mental State Examination scores and an increased likelihood of cognitive impairment.[135] However, other studies[136,137] failed to find the association.

Risks Faced by AD Offspring

We have not been able to find specific risk estimates for AD offspring in our survey of the literature.[14] One of the few studies focusing on AD offspring is the previously cited and ongoing multisite REVEAL study. In a series of randomized clinical trials of the predictive use of *APOE* testing, AD offspring and siblings have been provided risk information that incorporates *APOE* test results, and the psychologic and behavioral impact of this risk information on participants has been assessed up to 1 year after disclosure.[15] Results to date suggest that genetic risk information for AD, when delivered in a controlled research context by trained professionals, does not generally result in adverse psychologic effects among recipients. The study uses risk curves to clarify to participants the meaning of their *APOE* results.[85] In the absence of data specific for AD offspring, the risk curve estimates are based on family history data from other populations, such as the multicenter Multi-Institutional Research in Alzheimer's Genetic Epidemiology (MIRAGE) study of nearly 13,000 siblings and parents of AD patients and a 50-study pooled analysis of *APOE*-AD association in general populations. At this stage, like many other studies, REVEAL has no choice but to combine the risks for different types of first-degree relatives. However, discrepancies in frequencies obtained for parental as compared to sibling dementia, suggest that although it may be appropriate to use combined risk estimates for first-degree relatives when estimating purely genetic risks for developing AD, it may be suboptimal to do so when estimating the overall risk faced by AD offspring.

Today, AD offspring have unprecedented opportunities to apply potentially protective measures against AD. The recent decrease in heart disease and stroke, which may lead to a potential reduction in risk for AD, may be attributable at least in part to the availability of such new information. Putative protective measures against AD include improved diet and lifestyle, increased exercise, mental stimulation, social interaction, and the consumption of vitamins, nutraceuticals, and over-the-counter as well as prescription drugs (such as hormones, statins, and anti-inflammatory agents). Moreover, educational attainment, which seems to decrease risk of AD, has increased markedly over the last 2 generations. However, there are also risk factors that are on the rise. For example, the emerging epidemic of obesity may lead to increased risk of AD[138] and the consequences of the widespread substance abuse, beginning in the 1960s, remain unknown.

The genetic risk to AD offspring may thus be strongly modified by nongenetic factors that influence the timing of onset and ultimate expression of AD. Whether a factor will affect risk for AD may depend on the timing and duration of the exposure before onset of clinical symptoms. Because individuals genetically vulnerable to AD may not react in the same way as the general population in whom the risk and protective factors were identified, studies of risk and protective factors specifically within groups of AD offspring are urgently needed. In this context, it is important to point out that most of what is known about nongenetic risk and protective factors for AD has been obtained from studies in which the family history of participants is either unknown or poorly documented. As a result, potential interactions of familial status with other risk and protective factors have not been adequately examined.

In contrast to the general lack of data on protective factors in AD offspring, 2 prevention trials targeted first-degree relatives of AD patients: the Alzheimer's Disease Anti-inflammatory Prevention Trial (ADAPT) and the Preventing Postmenopausal memory loss and Alzheimer's with Replacement Estrogens (PREPARE) trial (see http://clinicaltrials.gov for study descriptions). An early report failed to detect significant differences in the ADAPT study.[139] Unfortunately, both trials were discontinued prematurely owing to concerns about drug safety (celecoxib and estrogen, respectively).

EARLY MARKERS

While awaiting clarification of interacting risk and protective factors, efforts are underway to identify markers that would be useful for early diagnosis of AD and for charting disease progression or regression in relation to therapeutic interventions. It is generally assumed that the earlier the detection, the greater the likelihood of arresting or reversing the course of AD. Optimally, AD markers would detect the disease early enough to prevent its manifestations. That goal is not as yet within reach, but ongoing research offers hope of achieving it. Below, we group the potential early markers currently being explored under the following 3 headings: cognitive performance, neuroimaging, and other potential early markers.

Cognitive Performance

Mild performance deficits on cognitive tests have been linked to increased risk of dementia in several short-term longitudinal studies of elderly samples.[140–148] These relationships have fueled attempts to define and characterize preclinical syndromes such as “mild cognitive impairment” (MCI) or “cognitive impairment, no dementia” (CIND) that may be useful for research with elderly samples.[149,150] There are disagreements among researchers as to how best to interpret such cognitive deficits. Some consider MCI a prodrome of AD or other forms of dementia,[151] whereas others point to the variable course and instability of psychometrically defined mild cognitive impairment.[152]

Only a few prospective studies have addressed the question of long-term predictive utility of cognitive tests. These studies have shown statistically significant associations between subclinical cognitive deficits or low levels of cognitive performance and increased risk of dementia across time spans as long as 10 to 20 years.[153–156] In these studies, baseline cognitive differences are very mild indeed, with mean scores of persons who eventually develop AD often falling in the low-average range. A related investigation, the well known “Nun Study,” documented an association between relatively low-idea density in samples of writing produced at an average age of 22 years and the diagnosis of dementia nearly 6 decades later.[157] None of these studies reported results for AD offspring as a distinct at risk group.

Table 1 lists longitudinal studies with neuropsychologic data on samples known to include AD offspring. The table is limited to US studies in which longitudinal cognitive data were already reported or are in the process of being collected, and it excludes studies that focused exclusively on relatives of patients with early-onset disease.[164,165] Representative publications are listed, but citations do not include all publications from a given study. To our knowledge, only 2 relatively small studies[158,159] reported longitudinal cognitive data for first-degree AD relatives and comparable controls without a family history of dementia; both are limited by their use of mixed offspring and sibling samples and retest intervals of only a few years. Additional studies of AD offspring are currently underway.

Several of the investigations summarized in Table 1 provide suggestive evidence that subclinical cognitive differences may be detectable by middle age. However, the relationship of these differences to clinical dementia remains to be clarified, as does the extent to which family history may affect predictive associations. To date, except for 1 small long-term follow-up,[19] longitudinal findings specific to children of AD parents have not been reported, and methods used to determine family history have often not been described. Direct documentation of AD in a parent by autopsy or research level clinical diagnosis is likely to yield a more accurate estimate of the increased risk of disease in offspring than family history interviews alone, particularly for a condition such as AD that may be easily confused with other dementing disorders.[166]

If reliable associations can be established between mid-life cognition and later dementia risk, several possible interpretations will need to be considered. Subtle mid-life difficulties with memory or attention could reflect relatively stable cognitive phenotypes that may persist with little change unless the individual begins to develop AD or other dementia. Alternatively, mild cognitive problems may correlate with underlying AD brain pathology (known to be present in mild extent for some individuals by early adulthood and to an increasing extent by age 50 and older), and may, therefore, reflect a true, albeit early, dementia prodrome.[96] For a discussion of cognitive prodrome vs. phenotype hypotheses, see Greenwood et al[18] and Sliwinski et al.[167]

Mid-life cognitive differences may also covary with health or environmental factors, which in themselves may be risk factors for AD.[157,168–170] Clearly, there is a danger of including individuals with preclinical dementia as "normal controls".[167] Only long-term prospective studies can clarify the meaning of mid-life cognitive differences, but in the near term, studies that relate cognitive performance to functional neuroimaging or other potential biomarkers are a high priority.

Neuroimaging

Functional neuroimaging methods are among the most promising approaches currently available for identifying possible early AD changes. Although these technologies are relatively new and continue to develop,[171] several research groups reported reduced rates of cerebral glucose metabolism (in brain regions known to be affected in AD) among clinically normal middle-aged[23,25,172] and younger adults with 1 or more *APOE* ε4 alleles. Differentiating patterns have also been documented with functional magnetic resonance imaging (fMRI) for *APOE* ε4 carriers and noncarriers.[23,173] Added to this are the findings from MRI volumetric studies that show smaller hippocampal size[174,175] and greater longitudinal decline in hippocampal volume for *APOE* ε4 carriers compared with controls.[176] It has recently been suggested that PIB (Pittsburgh Compound-B) amyloid imaging may be sensitive for detection of a preclinical AD state.[177,178] One patient came to autopsy 3 months after the PIB scan and the autopsy report confirmed the detection of β-amyloid by PIB.[179] According to the results of another study,[180] 2-(1-{6-[(2-[F-18]fluoroethyl)(methyl)amino]-2-naphthyl}ethylidene)malononitrile-PET (FDDNP) binding may be able to determine regional cerebral patterns of plaques and tangles and potentially distinguish persons with MCI or AD from normal controls. For these and other potential markers, longitudinal followup will be needed to determine how closely outcomes are linked to eventual development of AD.

For the study of AD offspring, 3 recent investigations provide particularly intriguing results. Strong family history effects, independent of *APOE* ε4 genotype, were observed in fMRI activation patterns among asymptomatic children of autopsy-confirmed AD patients[26] and in a second, independent sample of AD offspring where parental disease status was determined by autopsy, clinical assessment, or medical record review.[181] A third group reported distinctive fMRI findings for cognitively normal middle-aged adults with both an *APOE* ε4 allele and a family history of dementia, compared with persons with neither risk factor.[182] Specific findings have varied with different samples and study procedures. Considered together, however, these recent results suggest that failure to account for family history of AD in research samples may obscure potentially significant clues in the search for early markers of AD.

Other Potential Early Markers

Other potential markers of early AD include total tau in cerebrospinal fluid (CSF), phosphorylated forms of tau in CSF and plasma and also CSF β-amyloid, oligomeric forms

of β-amyloid, and isoprostanes.[183] In addition to candidate biomarkers, current proteomic and metabolomic technologies hold promise in the identification of formerly unknown biochemical markers of AD.[184,185] There are many more potential biomarkers for AD and some of these have already been investigated in a preliminary fashion such as plasma homocysteine,[186] CSF sulfatide,[187] α-1-antichymotrpysin,[188] and the ratio of *APP* isoforms in platelets.[189] However, because of the nonspecificity of some of the markers and the variability of others, only CSF markers of tau and β-amyloid have generated sufficient interest and scientific data to be considered viable biomarkers at this stage of development.[190] There is evidence that these CSF measures can be 80% to 90% accurate in establishing the diagnosis of AD versus controls.[191–193] Given that this rate is similar to what has previously been set as the autopsy standard,[194–198] this is remarkable progress for a test that is available during life when diagnostic issues are critically important to patients' treatment. However, to establish the predictive value of these and other potential biomarkers, they will have to be studied prospectively over extended periods of time in AD offspring. For example, although detection of PIB binding using nuclear imaging seems to be an indicator of the presence of amyloid pathology, the implications of PIB binding remain undefined for the future development of AD in asymptomatic persons.

Promising research currently underway in this area includes the NIMH's BIOCARD study,[162] the WRAP study,[16] the Washington University Adult Children study,[12] and studies of persons at risk for familial AD.[20,22,34] As these studies are in their early stages, long-term follow-up data are lacking. Prospective studies of AD offspring over extended periods of time are needed to determine the usefulness of these and other markers not only in early detection of AD but also in prediction of response to treatment and preventive interventions. Combining several possible preclinical markers (eg, amyloid imaging and CSF biomarkers[177] or risk factors[199]) to form risk profiles may be an especially powerful method for advancing predictive accuracy.

It is important to bear in mind that many (if not most) of the studies examining the biomarkers mentioned in this section on "Other Potential Early Markers" are restricted to "clean" subjects, that is individuals who are relatively healthy, without a history of head trauma and free from numerous specified medical comorbidities and medications. It is not clear how these selection criteria affected the results and to what extent the findings are applicable to general populations.

RESEARCH RECOMMENDATION

The brief survey provided above leads the authors to make the following recommendation together with 4 implementation strategies:

Devise strategies for assessing genetic and nongenetic risk and protective factors for the development of AD in children of AD parents. Whenever possible, use existing resources to achieve that goal in a cost-efficient and expeditious manner. In particular, utilization of data from prospective studies initiated 40 or more years ago may provide answers to some vital questions within years rather than decades. All strategies will require awareness of methodologic issues and collaboration among researchers at multiple sites to achieve adequate and representative samples. While doing so, consider children of AD parents, together with appropriate controls, as a potentially critical group to recruit for future prevention and intervention studies, especially those doubly at risk by virtue of family history of the disease and specific genotype (eg, *APOE* ε4).

Strategy 1: Use and build on available population studies and data resources, international and national. Organize data sharing with due consideration to ethical and

legal guidelines. Where it is possible to take advantage of existing data archives, results may be achievable within years rather than decades.

a. Build and maintain a comprehensive inventory of research projects currently studying risk and protective factors in samples that are known to include children of AD parents; identify adult children of AD parents within the samples of existing life course studies that have stockpiled appropriate data and have well-characterized AD in the parent sample; and encourage recruitment of adult children from other studies with well-defined populations that presently may not have a longitudinal design or a specific focus on dementia.

b. Include siblings and twins in addition to children of AD patients, to assess more thoroughly the effects of family history of AD on the development of AD. Accounting for generational differences and differences in years of vulnerability experienced by siblings as compared with children raises methodologic issues which need to be addressed. For comparative purposes, include children and siblings of parents without AD and without a family history of AD. Include longitudinal data on all participants and their relatives. Be sure to gather information on age or age at death for unaffected family members to fully characterize their status. For some analyses, it will be necessary to develop a repository of data to be used at a future time. For example, to compare risks associated with different first-degree relatives might require all probands and all first-degree relatives to be assessed at comparable ages.

c. Foster diversity in study populations, building on existing resources [eg, Sacramento Area Longitudinal Study on Aging (SALSA), WHICAP, Chicago Health and Aging Study, Indianapolis-Ibadan Study, ADAMS, the Alzheimer's Disease Research Centers (ADRCs) and Alzheimer's Disease Core Centers (ADCCs)].

d. Form a working group to review research design options and prioritize those research approaches that can evaluate the importance of family history in AD risk, within budget, time, and policy constraints, while controlling for other risk factors.

Strategy 2: Identify a common core of assessment procedures useful for the study of risk and protective factors, keeping instruments as brief as possible, whereas maintaining awareness of, and adapting to scientific advances whenever indicated.

a. Develop consensus regarding criteria for confirming AD in participants' parents. To maximize the yield from existing data, it may be useful for researchers to rank the likelihood that a study participant has a parent with AD on the basis of a continuum of certainty ranging from autopsy confirmation through research level clinical evaluation, review of existing medical records, and questionnaire or interview. Although each of these methods may yield useful information, prospectively documenting AD in a parent, using contemporary criteria, promises to more accurately reflect disease state than obtaining a family history based only on recall of events that occurred years, if not decades, earlier.

b. Develop consensus regarding criteria for selecting controls to compare with children of AD parents. A ranking of likelihood that a study participant's parents did not have AD or other dementia may also be useful, as the apparent absence of AD is highly linked to longevity and may be subject to other

detection biases. Ideally, the controls selected will have had both parents live for at least as long as the parents of the at risk offspring. Having access to current diagnoses, or autopsy diagnoses, would clearly improve ascertainment of controls.

c. Develop consensus regarding standardized collection of a common core of information on family history of dementia, race, ethnicity, and ancestry, and current and past lifestyle information (eg, medical, psychiatric, diet, medications, supplements, toxic exposures, mental and social stimulation, exercise, education, and occupation), on the basis of comprehensive review of existing questionnaires and interview methods.

Strategy 3: Explore the usefulness of preclinical changes in biologic measures, especially cognitive and neuroimaging, as early markers of AD.

a. Develop consensus regarding a common core of cognitive assessment instruments (or categories of instruments) useful for the study of preclinical change (eg, measures of memory and executive function, indices of literacy, quality and amount of education), that may be needed to adequately interpret results. Consideration should be given to identifying a small core of standardized tests that could be used across different studies and would be appropriate for ethnically and linguistically diverse populations. This core battery would be similar in principle to the Uniform Data Set[200] neuropsychologic battery of the ADRC and ADCC protocols, but should include measures that are sufficiently challenging to detect small performance differences in higher functioning at risk samples. Incorporation of a small number of experimental measures to increase sensitivity to subtle preclinical changes should also be considered.

b. Develop consensus regarding a common core of functional neuroimaging measures. Long-term longitudinal data on neuroimaging changes are lacking because some neuroimaging technologies have only recently been developed. It is important to determine what type of neuroimaging information exists in current databases and to incorporate neuroimaging measures into existing and new longitudinal studies of adult children of AD parents.

c. Develop consensus regarding the inclusion of a common core of biologic samples (eg, DNA, plasma, serum, urine, CSF, and lymphoblastoid cell lines) of highest priority for the study of AD offspring, specifying the goals of each type of sample. In the interest of efficiency and cost effectiveness, and keeping demands on research participants within reasonable limits, investigators will have to agree on a relatively small number of samples.

Strategy 4: Use all available analytic methods to address potential interactions between genetic and other risk and protective factors[201].

a. Encourage joint analysis of data from separate studies, including international and national resources.

b. Develop consensus on risk profiles, using information from multiple domains. In constructing such profiles, pay attention to parental AAO of AD and to the timing of exposure to putative risk and protective factors within the life courses.

c. Encourage testing of varying theoretical models of change, taking into account issues of temporal and longitudinal design.

CONCLUSIONS

Millions of children whose parents developed AD spend much of their adult lives wondering whether their future will include a fate like that endured by their parents. Despite the plethora of carefully conducted research studies, we still cannot predict with a satisfactory degree of certainty as to who among them will fall victim to the dreaded disease, nor even how many of them will eventually become afflicted. We do know that the risk of dementia increases exponentially with age. Most other suggested risk and protective factors still lack the robust data required for devising effective preventive and treatment interventions. Early markers to reliably identify vulnerable individuals are urgently needed. At risk individuals may benefit from current trials (www.alz.org) of potentially disease-modifying interventions. These trials depend on the voluntary participation of families with AD.

Although cross-sectional studies may be useful to determine if a given marker varies with genetic and/or other risk factors, prospective longitudinal investigations are needed to address the predictive value of putative AD markers and the time course to symptom expression. A handful of such studies are now underway, and given the age structure of the samples being studied, they may begin to provide a preliminary picture of risks to AD children within the next decade. If investigators involved in other ongoing longitudinal studies were to determine which of their participants are (or are not) offspring of parents with AD, this could greatly enlarge the pool of subjects and help to fast-track answers to at least some of the questions we identified. However, collaborative prospective, longitudinal studies achieving sufficiently large sample sizes, and using appropriate methodologies will allow us to take another step forward, that is to explore the complex interactions between individual vulnerabilities (genetic and nongenetic) and specific environmental variables. It is important to emphasize that, because of genetic-environmental interactions, the risk and protective factors identified within the general population may not apply to people with a family history of AD, or may operate in a different way. In view of mounting evidence of mid-life[168] and even earlier[157,169,170] risk factors for dementia, it will be important for some prospective studies to focus on these younger phases of life.

Clearly, further studies with AD offspring are bound to yield valuable insights. Because of the scientific discoveries of the past decades, the methodologies have become available. Now is the time to take advantage of them. For this reason, it is vitally important for children of AD parents to volunteer for research. It is precisely because of our lack of knowledge about risk and protective factors specific to this population that their help as research participants is potentially invaluable. While awaiting results of ongoing research, we urge the children of persons with AD to practice the lifestyle habits that promote good overall health and might perhaps reduce the risk of manifesting AD. We urge our colleagues to participate in initiating the much needed research outlined above.

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TABLE 1

Neuropsychologic Findings of Prospective Longitudinal Studies That Include First-degree Relatives of Persons With Alzheimer's Disease

Sample	Design/Procedures	Results/Comments
UCSD ADRC group[142]		
Nondemented elderly (mean age = 70 y), including some first-degree AD relatives	Cognitive results were based on short-term test-retest (three 1-y testings). This research group has also studied fMRI as a function of family history	AD relatives scored lower on verbal list learning measures, and 4 of 5 who converted to dementia in 3 y were AD relatives. Small sample and limited follow-up
UCLA/West LA VA Family Study of Alzheimer Disease[19,158]		
Nondemented first-degree AD relatives, young adult to middle-aged and matched controls without a family history of dementia. Above-average education	This study reported short-term cognitive test-retest (2 to 4 y) results for AD relatives versus controls, and 20-y cognitive outcomes for a small convenience sample (N = 25) of AD children that increased in age from 41 to 61 y; 44% were APOE ε4 positive	On short-term retest, a higher proportion of AD relatives showed cognitive decline than controls. Relatives of early-onset AD patients declined the most. At long-term follow-up, scores of AD children were generally stable compared with initial test scores and age norms. Small sample, limited follow-up, no controls reported for long-term follow-up
Family Studies of Alzheimer Disease (UCLA)[159,160]		
Nondemented healthy adults, mean age 60 to 65 y, including some first- degree AD relatives. Highly screened samples, high IQ and education	This research group has reported baseline cognitive data for family history negative and positive subjects, MRI and PET FDG, and short-term test-retest (2 y) results	Negligible familial vs. nonfamilial cognitive differences at baseline, despite some PET FDG differences. At retest, family history of AD predicted decline on a semantic retrieval task. Small samples and limited follow-up
U. Arizona/Mayo-Scottsdale[24,161]		
Nondemented ε4 carriers vs. noncarriers, middle-aged. Most subjects had first-degree relatives with AD	This research group has reported short-term test-retest (2 to 3 y) cognitive data and volumetric MRI and PET results	No difference for APOE groups at baseline on any cognitive dimension. In the most recent report with the largest sample, memory decline over time was greater for the ε4 group, especially on a verbal list learning test. Brain metabolic differences observed for APOE groups at baseline and over time
NIMH BIOCARD Study[18,162,163]		
Nondemented adults, 50–79 y. Most had first-degree relatives with AD	This group has reported baseline cognitive results and short-term (3 y) test- retest findings, focused primarily on experimental attention tasks and selected clinical memory tasks	ε4 carriers, especially homozygotes, had reduced visuospatial attention, visual working memory, and delayed story recall at baseline, compared with noncarriers. Attentional scaling diverged longitudinally, with genotypes 2/4 and ε4/4, but not 3/4, showing a decline in performance over time
WRAP[16]		
Through October, 2007, 820 middle-aged children of parents with AD and 305 controls whose parents were dementia-free have entered the study, and enrollment is continuing. AD in parents was identified by memory-clinic evaluation, autopsy, or record review	Only baseline data reported to date. In addition to cognitive testing, study procedures include blood and CSF assays, genetic analyses including APOE genotype, and fMRI. First 4-y retest began in 2006	No differences in baseline neuropsychologic performance for AD relatives vs. controls, or for ε4 carriers vs. noncarriers. However, fMRI differences were observed in this sample as a function of family history
Washington University Adult Children Study[12]		
Currently enrolling children of AD parents and controls with parents free of dementia. Presence of AD in the parent has been established through long-term longitudinal follow-up in the Memory and Aging Study and/or autopsy	In addition to cognitive testing, study procedures include PET with Pittsburgh Compound B, blood and CSF assays, genetic analyses including APOE genotype, structural MRI, and personality testing	No neuropsychologic results reported as yet
Framingham Offspring Study[17]		

Sample	Design/Procedures	Results/Comments
Incident cases of AD have been identified within the original Framingham Heart Study cohort through long-term longitudinal follow-up. Children of the original cohort and their spouses comprise the Offspring Study, initiated in 1971. Between 1999 and 2003, 1400 offspring, including >200 with a parent who had AD, had brain MRI and neuropsychologic testing. There is also a comparison group of offspring whose parents remained free of dementia	Cognitive testing and brain MRI	No published neuropsychologic outcomes as yet

UCLA indicates University of California, Los Angeles; UCSD, University of California, San Diego.