Published in final edited form as:
J Geriatr Psychiatry Neurol. 2005 December ; 18(4): 192–195.

Predicting Alzheimer's disease in the Baltimore Longitudinal Study of Aging

Alan B Zonderman
National Institute on Aging, Laboratory of Personality & Cognition, Cognition Section

Abstract

Longitudinal studies offer opportunities for studying children whose parents have Alzheimer's disease. The Baltimore Longitudinal Study of Aging (BLSA) has examined adult cognitive performance but has not systematically recruited participants' children. We initiated studies of dementia in the 1980's. This work suggested that hormone replacement and use of non-steroidal anti-inflammatory drugs reduced the risk of Alzheimer's disease, and risk for Alzheimer's disease could be predicted from cognitive performance as many as 20 years prior to its onset. More recently, we showed that premorbid levels of free testosterone were lower in men who developed Alzheimer's disease and premorbid depressive symptomatology was a risk for Alzheimer's disease in men but not women as many as 6 years before the onset of dementia. Participants in the BLSA include family members with a variety of degrees of relationship, but there is no systematic effort to collect data from relatives of participants.

Keywords

Alzheimer's disease; dementia; prospective study; longitudinal follow-up study; aging; risk factors

Existing longitudinal studies may offer new opportunities for studying children whose parents have Alzheimer's disease, particularly when parents are participants in long-term projects with many repeated assessments. The Baltimore Longitudinal Study of Aging (BLSA) is an example of a long-term study in which family relatives may participate but for which there has not been systematic recruitment of participants' children. Designed in 1958 as a study "to trace the effects of aging in humans,"[1] the BLSA recruited community-dwelling men aged 17 to 96, and women beginning in 1978, to participate in repeated assessments of health and physical and psychological performance. Intervals between repeated assessments have varied over the course of the study. Over time, the cohort of participants in the BLSA has varied considerably. BLSA participants are a sample of convenience. The study recruited new participants as others dropped out or as there were additional resources to test more people. Initially, "visits" to the BLSA occurred every two years and participants were examined over the course of 2½ days. Intervals between assessments were revised with the increasing recognition that trajectories of change may occur more rapidly in older participants than younger participants. Presently, the protocol re-tests everyone younger than 50 every four years, those aged 50 to 79 every two years, and everyone 80 and older every year.

Measures of cognitive performance were introduced into the BLSA in 1960. The purpose of the cognitive assessments was to measure the pattern of change – if any – in cognitive abilities over the adult life span. The history of cognitive testing from its inception through the

Address correspondence to Alan Zonderman, National Institute on Aging, Gerontology Research Center, 5600 Nathan Shock Drive, Baltimore, MD 21224,Zonderman@nih.gov.

mid-1980's has been summarized elsewhere[1, 2]. Beginning in 1985, neuropsychological tests were introduced specifically for diagnosing dementia in the BLSA cohort[3].

Predicting Alzheimer's disease

Although the BLSA is a convenience sample, the incident rates of Alzheimer's disease are consistent with published rates from other studies[3]. For approximately 13 years between January 1985 and May 1998, 155 cases of dementia were diagnosed from a pool of 1236 participants (802 men, 434 women). Of the 155 cases of dementia, 114 (74%) participants were diagnosed with Alzheimer's disease. The average length of follow-up was 7.5 years. Diagnoses of Alzheimer's disease were based on DSM-III-R[4] and NINCDS-ADRDA[5] criteria. As expected, the age-specific incidence increased significantly with age, and incidence rates was similar to other studies. This suggests that despite BLSA's non-representational sampling methods, the wealth of longitudinal data has significant value for long-term predictions of AD.

A central interest in our studies of cognitive aging is predicting the onset of dementing disorders. Based on initial diagnoses, we examined the differences between participants who were ultimately diagnosed with Alzheimer's disease and those with no such diagnosis using retrospective data on visual memory. We examined whether six-year changes in immediate visual memory performance assessed by the Benton Visual Retention Test[6] predicted Alzheimer's disease prior to its onset[2]. In these early data, there were 371 BLSA participants, seven of whom were diagnosed as probable or definite Alzheimer's disease. Six-year longitudinal change as well as level in immediate visual memory performance also predicted subsequent cognitive performance 6–15 and 16–22 years later, even after adjusting for the influences of age, general ability, and initial immediate memory. In a subsequent follow-up to these findings in a larger sample, we examined premorbid neuropsychological test scores in order to determine whether long term deficits in the Benton Visual Retention Test predicted the development of Alzheimer's disease decades later[7]. The relative risks for Alzheimer's disease associated with making 6 or more visual memory errors versus less than 6 errors at 1 to 3, 3 to 5, 5 to 10, and 10 to 15 years before the diagnosis of Alzheimer's disease were 5.69, 2.11, 1.76, and 1.83 respectively ($p<0.05$). The relative risk for 15 or more years before diagnosis was not significant.

Hormones

Previous reports suggested that hormone therapy in post-menopausal women may exert a protective effect on the risk of developing Alzheimer's disease[8]. After documenting hormone therapy status prospectively at each BLSA visit, we categorized 472 post-menopausal women followed for up to 16 years who had used oral or transdermal estrogens at anytime as hormone therapy users. Using Cox proportional hazards with time-dependent covariates, we estimated the relative risk for Alzheimer's disease after hormone therapy compared with women who had not used hormone therapy. After adjusting for education, the relative risk for Alzheimer's disease in hormone replacement users compared with nonusers was 0.46 (95% CI 0.219–0.997). This suggests a reduced risk for Alzheimer's disease in women who had reported the use of hormone therapy. More recently, randomized clinical trials from the Women's Health Initiative Memory Study have shown that hormone therapy is *not* beneficial in reducing the risk for dementia or mild cognitive impairment, and in fact may increase their risk[9, 10].

We also investigated the relationships between age-associated decreases in endogenous serum total testosterone and free testosterone index and the subsequent development of Alzheimer's disease in 574 men[11]. Men in this study were 32–87 years old at baseline, and they were all free of Alzheimer's disease at their baseline testosterone assessments. We assessed participants at multiple time points and we re-examined them periodically for a mean of 19.1 years (range, 4 to 37 years). Diagnosis of Alzheimer's disease was associated inversely with free testosterone

index by itself after adjusting for age, education, smoking status, body mass index, diabetes, any cancer diagnoses, and hormone supplements. The results for the lagged analyses were nearly identical suggesting that low free testosterone was a risk for Alzheimer's disease and was not a consequence of Alzheimers disease. Increases in the free testosterone index were associated with decreased risk of Alzheimer's disease (hazard ratio = 0.74; 95% CI = 0.57 to 0.96), a 26% decrease for each 10-nmol/nmol increase in the free testosterone index. These results suggest that calculated free testosterone concentrations were lower in men who developed Alzheimer's disease, and this difference occurred before diagnosis.

Inflammation

We examined whether the risk of Alzheimer's disease was reduced among reported users of aspirin or other nonsteroidal anti-inflammatory drugs[12]. The relative risk for Alzheimer's disease decreased with increasing duration of nonsteroidal anti-inflammatory drug use. Among those with 2 or more years of reported use of nonsteroidal anti-inflammatory drugs, the relative risk was 0.40 (95% CI 0.19–0.84) compared with 0.65 (95% CI 0.33–1.29) for those with less than 2 years of use. The overall relative risk for Alzheimer's disease among aspirin users was 0.74 (95% CI 0.46–1.18), and there was no trend for decreasing risk of Alzheimer's disease with increasing duration of aspirin use. There was no association between Alzheimer's disease risk and use of acetaminophen, and there was no trend of decreasing risk with increasing duration of use. These results were consistent with evidence from cross-sectional studies indicating reduction of risk for Alzheimer's disease associated with use of nonsteroidal anti-inflammatory drugs, and consistent with evidence suggesting that one stage of the pathophysiology leading to Alzheimer's disease is characterized by an inflammatory process[13].

Depression

Depression is associated with increased risk for dementia and Alzheimer's disease, although it is unclear whether it represents an actual risk factor or a prodrome[14]. It is unclear how often mild cognitive impairment seen in non-demented depressed elderly individuals develops into subsequent cognitive decline and dementia. However, depressive symptoms are common in patients with Alzheimer's disease, especially in early stages of the disease. To determine the relative hazard of premorbid depressive symptomatology for development of dementia and Alzheimer's disease, we studied the risk for incident dementia and Alzheimer's disease over 14-years in 1,357 participants in the Baltimore Longitudinal Study of Aging.

Using time-dependent proportional hazards, we performed separate analyses predicting the development of Alzheimer's disease or dementia on men and women at three separate intervals before the onset of dementia symptoms. We performed both unadjusted and adjusted analyses using covariates associated with vascular disease. Covariates included education, clinical diagnoses of heart disease, hypercholesterolemia, hypertension, cerebrovascular disease, diabetes, and obesity. We assessed depressive symptoms by the Center for Epidemiologic Studies – Depression Scale (CES-D), a measure widely accepted in epidemiologic studies of depression in general populations. The CES-D correlates strongly with other self-reported depression inventories and with variables related closely to clinical diagnoses of depression. A standard cutoff score of 16 or greater has been validated as indicating clinically significant depressive symptoms, identifying many individuals with major depressive disorders.

Because depressive symptoms could be a consequence of Alzheimer's disease, we performed these analyses with various lagged intervals between last measure of depressive symptoms and age of diagnosis or censoring. Premorbid depressive symptoms significantly increased the risk for Alzheimer's disease in men but not in women. The risk for Alzheimer's disease associated with depressive symptoms in men was two times greater than risk for men without depression,

and did not vary as the lag between detection of symptoms and diagnosis of dementia was increased. This suggested that prodromal dementia was not the cause of the affective symptomatology. Hazard ratios were approximately two times greater than for men without history of depressive symptoms even after adjusting for the covariates. This suggests that the effect was independent of vascular disease. These results suggest that the effect of depressive symptoms on risk for Alzheimer's disease may vary with sex, and it is unlikely that depressive symptoms are a prodrome for Alzheimer's disease.

Children of Alzheimer's Disease Parents

Participants in the Baltimore Longitudinal Study of Aging include family members with a variety of degrees of relationship, including spouses and parents. There has been no systematic effort to collect data from individuals related to participants. The lone exceptions are studies that rate participants' personalities or symptoms of dementia. These studies have shown that participants' relatives are equally cooperative in volunteering for clinical studies.

The Baltimore Longitudinal Study of Aging is a potentially rich source for performing family studies of adult children. Presently, there are approximately 600 men and women who are active participants in the study with follow-up cognitive assessments. Historically, there are over 1,000 men and women with follow-up data, approximately 150 of whom have diagnoses of Alzheimer's disease.

There are advantages to basing a study of children whose parents have Alzheimer's disease on an existing longitudinal study, particularly a study with long-term repeated assessments. Perhaps the greatest advantage is that with sufficient repeated data, it is possible to compare parents' cognitive trajectories with their children's trajectories. Multidisciplinary studies such as the BLSA have a variety of physiological data, often including stored biomaterials such as serum, plasma, and urine with which we can compare parents' biomarker assays over time with their children's assays at the same ages. As an ongoing study, the BLSA has the infrastructure to invite children of existing participants to join the study. This is particularly important because tracing and re-contacting study participants are the largest barriers to follow-up assessments in terminated studies.

It would take considerable work to examine the children of these participants. Although our study is based in Baltimore, many of the participants do not reside in or near Baltimore. We have no data on the geographical dispersal of participants' children. It is unlikely that they are concentrated in Baltimore. However, it is possible that participants' children will be as enthusiastic to volunteer as their parents were. For more than a decade, we have found that participants who were unable to travel to Baltimore for repeated assessments were willing to be tested in their homes.

The BLSA is one of several longitudinal studies that may offer opportunities to establish ancillary research on children whose parents have Alzheimer's disease. For example, other national and international longitudinal studies may offer a rich source of parallel data on parents and children. There are a variety of studies from which to choose such as The Duke Longitudinal Study of Normal Aging[15], the Established Populations for Epidemiologic Studies of the Elderly[16], the Berlin Aging Study[17], and the Canberra Longitudinal Study[18]. The latter has already used a survey to examine Alzheimer's disease in first-degree relatives.

References

1. Shock NW, Greulich RC, Andres R, et al. *Normal Human Aging: The Baltimore Longitudinal Study of Aging* Washington, DC.: NIH Publication No. 84-2450, U.S. Government Printing Office; 1984.

2. Zonderman AB, Giambra LM, Arenberg D, Resnick SM, Costa PT Jr, Kawas CH. Changes in immediate visual memory predict cognitive impairment. Arch Clin Neuropsychol 1995;10:111–123. [PubMed: 14589733]
3. Kawas C, Gray S, Brookmeyer R, Fozard J, Zonderman A. Age-specific incidence rates of Alzheimer's disease: The Baltimore Longitudinal Study of Aging. Neurology 2000;54:2072–2077. [PubMed: 10851365]
4. American Psychiatric Association. *Diagnostic and statistical manual of mental disorders, 3rd edition, revised* Washington, DC: American Psychiatric Association; 1987.
5. McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. Neurology 1984;34:939–944. [PubMed: 6610841]
6. Benton AL. *The revised Benton Visual Retention Test* New York: Psychological Corporation; 1974.
7. Kawas CH, Corrada MM, Brookmeyer R, et al. Visual memory predicts Alzheimer's disease more than a decade before diagnosis. Neurology 2003;60:1089–1093. [PubMed: 12682311]
8. Kawas C, Resnick S, Morrison A, et al. A prospective study of estrogen replacement therapy and the risk of developing Alzheimer's disease: the Baltimore Longitudinal Study of Aging. Neurology 1997;48:1517–1521. [PubMed: 9191758]
9. Shumaker SA, Legault C, Rapp SR, et al. Estrogen plus progestin and the incidence of dementia and mild cognitive impairment in postmenopausal women: the Women's Health Initiative Memory Study: A randomized controlled trial. JAMA 2003;289:2651–2662. [PubMed: 12771112]
10. Shumaker SA, Legault C, Kuller L, et al. Conjugated equine estrogens and incidence of probable dementia and mild cognitive impairment in postmenopausal women: Women's Health Initiative Memory Study. JAMA 2004;291:2947–2958. [PubMed: 15213206]
11. Moffat SD, Zonderman AB, Metter EJ, et al. Free testosterone and risk for Alzheimer disease in older men. Neurology 2004;62:188–193. [PubMed: 14745052]
12. Stewart WF, Kawas C, Corrada M, Metter EJ. Risk of Alzheimer's disease and duration of NSAID use. Neurology 1997;48:626–632. [PubMed: 9065537]
13. Akiyama H, Barger S, Barnum S, et al. Inflammation and Alzheimer's disease. Neurobiol Aging 2000;21:383–421. [PubMed: 10858586]
14. Dal Forno G, Palermo MT, Donohue JE, Karagiozis H, Zonderman AB, Kawas CH. Depressive symptoms, sex, and risk for Alzheimer's disease. Ann Neurol Feb 24;2005 57(3):381–387. [PubMed: 15732103]
15. Palmore EB. *Normal aging* Durham, N.C.,: Duke University Press; 1970.
16. Cornoni-Huntley J, Ostfeld AM, Taylor JO, et al. Established populations for epidemiologic studies of the elderly: Study design and methodology. Aging (Milano) Feb;1993 5(1):27–37. [PubMed: 8481423]
17. Smith J, Maas I, Mayer KU, Helmchen H, Steinhagen-Thiessen E, Baltes PB. Two-wave longitudinal findings from the Berlin aging study: introduction to a collection of articles. J Gerontol B Psychol Sci Soc Sci Nov;2002 57(6):P471–473. [PubMed: 12426428]
18. Korten AE, Jorm AF, Henderson AS, Broe GA, Creasey H, McCusker E. Assessing the risk of Alzheimer's disease in first-degree relatives of Alzheimer's disease cases. Psychol Med Nov;1993 23(4):915–923. [PubMed: 8134515]