

# HAS FAMILIAL AGGREGATION IN ALZHEIMER'S DISEASE BEEN OVERESTIMATED?

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## ABSTRACT

Studies of the familial aggregation of Alzheimer's disease have primarily used samples ascertained from tertiary care clinics which may not be representative of many AD patients, for example those residing at geriatric nursing homes. Survival analysis was used to investigate whether estimates of familial aggregation of AD based on a clinic-based AD proband (C-AD) sample (probands:  $N = 544$ ; first degree relatives:  $N = 4267$ ) differ from one ascertained at a nursing home (NH-AD; probands:  $N = 225$ ; first degree relatives:  $N = 1772$ ). The cumulative survival from AD was significantly worse in relatives of the C-AD probands and the overall relative risk (RR) of AD in this group was greater than twice that of relatives of the NH-AD probands. However, age at onset in C-AD probands was significantly earlier than in the NH-AD group and in both groups this factor was negatively associated with familial aggregation. When, for this reason, the proband samples were matched one-to-one by age at onset, dropping those probands with no match, the two curves were close to identical and the RR for the C-AD group of relatives was 1.0. The results suggest that estimates of familial risk of AD based on C-AD samples are not applicable and overestimate the extent of increased risk for relatives of more prevalent, later onset AD probands. However, the overestimate can be explained by the typically earlier age at onset in C-AD samples as opposed to a sampling bias related to the proband's family history status per se. The relationship between onset age and familial aggregation suggests that no single estimate of the age-dependent risk (survival curve) is uniformly appropriate for relatives of AD probands. Copyright © 2000 John Wiley & Sons, Ltd.

KEY WORDS—dementia; age on onset; survival analysis

## INTRODUCTION

Several genes are now known to either directly cause Alzheimer's disease (AD), in a very small fraction of cases, or increase the risk of the disease, in a far larger proportion (Levy-Lehad *et al.*, 1995; Saunders *et al.*, 1993; Tanzi *et al.*, 1993). Beyond the genes already identified, family history studies of AD indicate the presence of additional powerful, but as yet unidentified familial/genetic factors (Farrer *et al.*, 1995; Li *et al.*, 1996). These familial aggregation studies of AD have primarily relied on

patient samples derived from clinics associated with academic research centers (Lautenschlager *et al.*, 1996; Li *et al.*, 1991; Silverman *et al.*, 1994a) and such samples may not wholly represent the larger AD population. It is certainly the case, for example, that most AD probands in clinic-based studies (C-AD) have onset ages that are markedly earlier than one would expect from the overall incidence of AD which appears to peak after age 85 (Hebert *et al.*, 1995). It is unclear, however, whether such samples have increased familial aggregation compared with an AD proband sample whose families have not actively sought out treatment from a tertiary medical care center. Dementia is a common and still a generally unremediable condition of old age and the treatments that are available are frequently unknown to primary care physicians who also tend to underdiagnose the condition (Brodaty *et al.*, 1994). These factors may contribute to a select group of

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patients and families who seek tertiary clinical care. It is possible that the presence of a previously affected relative may increase a family's or patient's desire for more aggressive evaluation and treatment options. In contrast, placement of demented residents into chronic care facilities is usually related to severity of dementia or lack of appropriate outpatient support services. This leads to the hypothesis that there is biased ascertainment in geriatric clinics due to the familial characteristics of the proband and, hence, greater familial loading for AD among AD probands ascertained in a specialized geriatric clinic compared with those ascertained in a chronic care facility.

The disproportionate number of early onset cases in clinic-based samples complicates testing this hypothesis. Onset age is negatively associated with increased familiarity of AD (Heun and Maier, 1995; Lautenschlager *et al.*, 1996; Li *et al.*, 1995; Silverman *et al.*, 1994a). Thus, a clinic sample might have a relatively increased familial aggregation owing to the over-representation of early onset cases, unrelated to a bias directly due to the familial characteristics of a proband. However, whether because of characteristics of treatment seeking families or proband age at onset, if the risk of AD in relatives in C-AD probands is inflated, then the true familial risk of typical AD may be lower than has been generally observed in studies to date, relying as they have on primarily C-AD samples. To clarify this issue, the present study compared the familial aggregation of AD in AD probands from a clinic-based sample with familial aggregation of AD in AD probands in a nursing home population, with and without consideration of the age at onset in the AD proband.

## METHODS

### *Probands*

The C-AD probands were ascertained from consecutively evaluated outpatients meeting the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria for probable AD (McKhann *et al.*, 1984) in the memory disorders clinic at Mt. Sinai, Bronx Veterans Affairs, and Elmhurst General Hospitals. Some of the probands in the present sample were included in previous reports (Silverman *et al.*, 1994a), but there

is no overlap with other studies focusing on the questions examined here. The nursing home sample of AD probands (NH-AD) was ascertained from a list of current Jewish Home and Hospital for Aged (JHHA) residents with an AD diagnosis ordered by their institutional ID number determined in part by their admission time. The JHHA is a 1300 bed nursing home facility with sites in Manhattan and the Bronx. A subset of the NH-AD sample was clinically evaluated for AD based on NINCDS-ADRDA criteria for probable AD by a diagnostic team supervised by the same clinician (DBM) who supervises C-AD diagnoses. The majority of probands, however, were diagnosed through direct clinical assessment by geriatric physicians using ICD-9 criteria. Because this diagnostic procedure was used for most NH-AD probands, we first compared the two NH-AD subsamples in terms of their demographic and familial characteristics before making the larger comparison between C-AD and NH-AD samples.

### *Assessment of first degree relatives*

As described in detail elsewhere (Silverman *et al.*, 1994a), first degree relatives of AD probands were identified using the Alzheimer's Disease Risk Questionnaire (ADRQ) (Breitner and Folstein, 1984). For each relative, this instrument was also used to collect the birth year, sex, current age or age at and cause of death, and to screen for possible dementia, cognitive impairment, or memory loss of any type. If any such condition was suggested, the Dementia Questionnaire (DQ) was administered for that relative to assess for AD (Silverman *et al.*, 1986). The DQ is a 50 item questionnaire focused on ascertaining whether a dementia is present and, if so, determining its specific type. Relatives were classified as AD according to previously published criteria (Silverman *et al.*, 1990) similar to DSM-IV criteria for Dementia of the Alzheimer's Type, but modified for informant based assessment. Previous studies of this assessment methodology have found very good inter-informant (Silverman *et al.*, 1986) and test-retest reliability (Silverman *et al.*, 1990). The DQ has demonstrated excellent sensitivity and specificity for identifying dementias in a group of elderly independently ascertained through direct clinical assessment (Kawas *et al.*, 1994). In addition, in a study of a series of former nursing home residents, the informant-based DQ diagnoses were compared with independent neuropathological examinations;

the family history method's sensitivity for AD was found to be only slightly less strong than direct clinical assessment and its specificity was virtually at the same level (Li *et al.*, 1997).

### Statistics

In addition to conventional chi-square and students *t*-tests, we used actuarial life table method to construct cumulative survival curves for each group. These curves were compared using the log rank test. The Cox proportional hazards model was used to assess the relative risk (RR) of AD in the family members of the C-AD probands using the relatives of the NH-AD proband sample as the reference group. The Wald statistic was used to test the null hypothesis that the population regression coefficient is equal to zero (Klein and Moeschberger, 1997).

## RESULTS

Diagnostic assessments were collected on 4267 first degree relatives of 544 C-AD probands and 1772 first degree relatives of 225 NH-AD probands. Table 1 provides demographic data on the two proband groups as well as their respective relatives. In addition, Table 1 provides the same information in the two subsamples of the NH-AD probands, i.e. those diagnosed either by NINCDS or ICD-9 criteria.

The two NH-AD subsamples were first com-

pared in order to examine whether the two diagnostic methods used in this group led to different characteristics in the probands or their families. The two subsamples were similar to each other with respect to each of the categories considered (all *ps* > 0.30): proband age-at-onset, age at interview and sex, as well as the probands' relatives' age, sex, the proportion of AD cases among relatives, and the age-at-onset of those cases. The survival curves associated with the relatives of the two subsamples were also very similar (log rank = 0.01, d.f. = 1, n.s.). For example, cumulative survival from AD by age 90 was  $0.831 \pm 0.024$  and  $0.837 \pm 0.058$  in the relatives of NH-AD probands diagnosed by ICD-9 versus NINCDS, respectively. Using the Cox proportional hazards model, we then compared the rates of familial aggregation in the two NH-AD groups which were found to be virtually identical (Wald statistic = 0.006, d.f. = 1, n.s.; RR = 1.0). Finally, the results, reported below, using the full NH-AD proband series in the subsequent comparisons with the C-AD groups were essentially the same when either one of these two subgroups were used alone.

The C-AD group was then compared with the full NH-AD group. As shown in Table 1, the C-AD probands had a significantly earlier age at onset, were younger at the time of interview, and were less frequently female than the NH-AD probands. The relatives in the two proband groups were both evenly divided by sex. However, the relatives of the C-AD probands were significantly younger, showed a trend level increased number

Table 1. Demographic and disease characteristics of C-AD and Nh-AD probands and their first degree relatives\*

Proband group	Proband				First degree relatives				
	<i>N</i>	Onset†	Age‡	Female (%)§	<i>N</i>	Age¶	Female (%)	AD**	Onset††
C-AD	544	69 ± 10	73 ± 9	315 (57.8)	4267	57 ± 23	2164 (50.7)	236	72 ± 15
NH-AD	225	80 ± 10	88 ± 7	176 (78.2)	1772	60 ± 28	873 (49.4)	77	76 ± 17
ICD-9	176	81 ± 10	88 ± 7	144 (81.8)	1517	60 ± 28	744 (49.0)	68	76 ± 18
NINCDS	49	82 ± 9	88 ± 7	43 (87.8)	255	58 ± 28	129 (50.6)	9	80 ± 8
Total	769	72 ± 11	78 ± 11	491 (63.8)	6039	58 ± 25	5037 (50.3)	313	73 ± 16

\* Statistical comparison indicated below refer to overall comparisons between C-AD and NH-AD groups. Comparisons within the NH-AD group by ICD-9 versus NINCDS were all nonsignificant (all *ps* > 0.30).

† *t* = 14.86, d.f. = 721, *p* < 0.001.

‡ *t* = 21.51, d.f. = 709, *p* < 0.001.

§  $\chi^2$  = 28.47, d.f. = 1, *p* < 0.001.

¶ *t* = 4.81, d.f. = 6016, *p* < 0.001.

||  $\chi^2$  = 0.88, d.f. = 1, n.s.

\*\*  $\chi$  = 3.58, d.f. = 1, *p* = 0.06.

†† *t* = 2.24, d.f. = 310, *p* < 0.05.

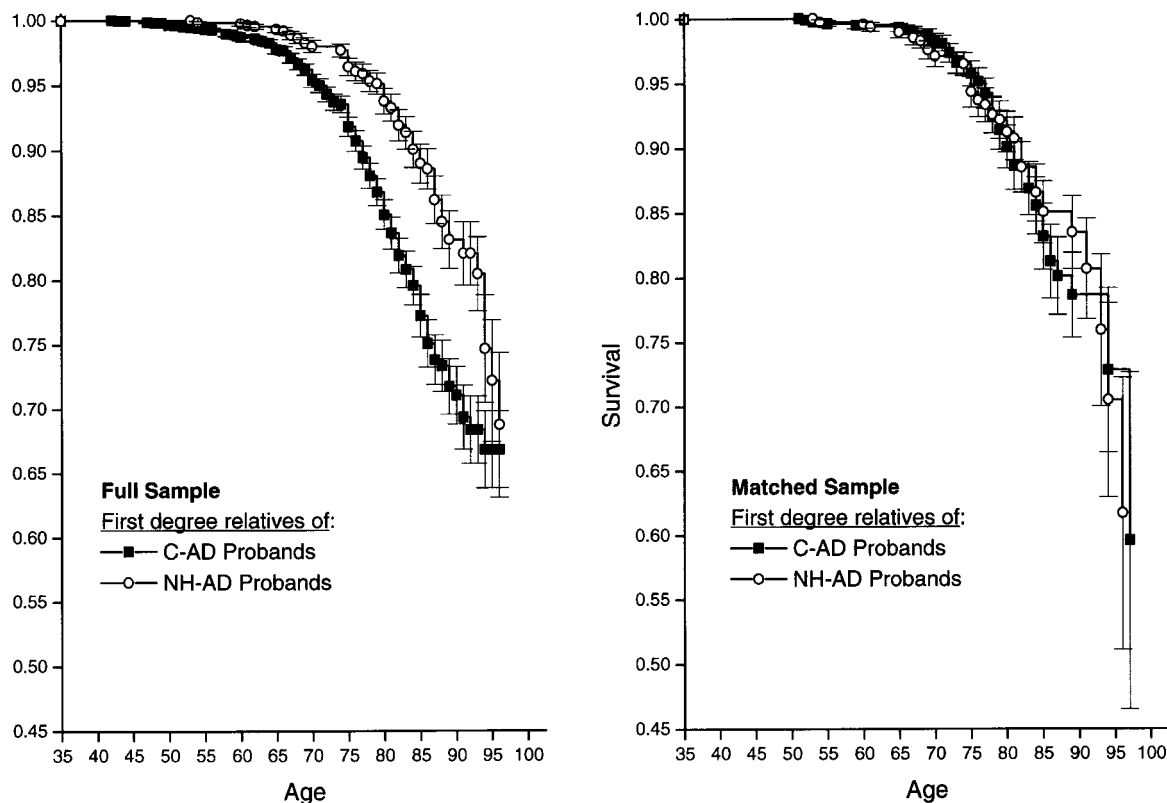


Fig. 1. (a) Cumulative survival from AD in first degree relatives of all C- (filled squares) and NH- (open circles) AD probands. (b) Cumulative survival from AD in first degree relatives of C- (filled squares) and NH- (open circles) AD probands matched for age at onset

of AD cases and, among such cases, a significantly earlier age at onset.

Life tables showing the cumulative risk of AD were constructed for the two relative groups (Fig. 1a). The survival curve in the relatives of the C-AD probands fell earlier and more steeply than the relatives of the NH-AD probands and the two curves were significantly different (log rank = 31.56, d.f. = 1,  $p < 0.0001$ ). By age 90, the cumulative risk of AD among relatives of C-AD probands was  $71.7\% \pm 2.2\%$ , significantly lower ( $z = 3.67$ ,  $p < 0.001$ ) than the cumulative survival among relatives of NH-AD probands at the same age,  $83.1\% \pm 2.2\%$ . The marked discrepancy in survival curves was diminished only at the very latest ages of newly identified cases ( $> \text{age } 92$ ), but reduced sample sizes in the tenth decade makes these last estimates uncertain. The Cox pro-

portional hazards model was then used to compare the overall extent of the increased risk of AD among relatives of the C-AD proband sample against the relatives of the NH-AD proband sample. Relatives of the C-AD probands had more than twice the overall risk of AD than relatives of the NH-AD probands (Wald statistic = 30.0, d.f. = 1,  $p < 0.0001$ , RR = 2.1 [95% CI: 1.6, 2.7]).

Proband age at onset has been previously negatively associated with risk of AD among relatives and this relationship was present in both the C-AD and NH-AD groups (C-AD: Wald statistic = 36.4, d.f. = 1,  $p < 0.0001$ ; RR = 0.96 [95% CI: 0.95, 0.97]; NH-AD: Wald statistics = 5.6, d.f. = 1,  $p < 0.05$ ; RR = 0.98 [95% CI: 0.96, 1.00]). For this reason, we matched probands from the two groups one for one by age at onset, excluding those probands in one group with no uniquely

corresponding proband in the other group with the same onset age. We used computer generated random numbers to select probands in those cases when there were more probands in one group to match with the other. This created two groups each with 131 probands and a mean onset age of 77 years  $\pm$  7 years and comparable numbers of relatives (C-AD group:  $N = 1019$ ; NH-AD group:  $N = 952$ ). Again, AD cumulative survival curves were constructed (Fig. 1b). This time the two curves were highly similar (log rank = 0.04, d.f. = 1, n.s.). Also in contrast to the full sample comparison, using the matched sample, the Cox proportional hazards model provided no evidence for increased RR among the relatives of the C-AD probands (Wald statistic = 0.04, d.f. = 1, n.s., RR = 1.04 [95% CI: 0.70, 1.55]).

## DISCUSSION

Without statistically controlling for proband age at onset, familial aggregation of AD was observed to be more than twice as strong among C-AD than NH-AD proband families. Particularly with respect to their age at onset characteristics, the NH-AD proband sample is more representative of the overall population of AD patients than is the C-AD sample which tends to have younger probands with earlier onset of disease. Investigations of risk to relatives of AD probands, however, have primarily employed less typical, clinic-based samples (Lautenschlager *et al.*, 1996; Li *et al.*, 1991; Mayeux *et al.*, 1991; Silverman *et al.*, 1994a,b) and have found rates of survival from AD among relatives at levels comparable to what was observed in the relatives of the C-AD sample. For example, in the largest familial aggregation study of the AD to date (Lautenschlager *et al.*, 1996), survival from AD by age 90 was 67.1% among the relatives of AD probands ascertained from clinic populations, comparatively close to the 71.7% survival observed in the relatives of the present C-AD sample, but markedly worse than the 83.1% survival in the relatives of the NH-AD sample. The results of the present study suggest that risk estimates based on clinically ascertained samples substantially overstate the risk in relatives of the more typical, but less frequently studied, very late onset AD probands.

At the same time, the present results suggest that the increased familial aggregation in C-AD and NH-AD proband families is not directly attribu-

table to an increased likelihood for more familial cases of AD to seek tertiary medical care, but instead can be explained by onset characteristics of the cases treated by such facilities. As expected, age-at-onset was significantly earlier in the C-AD group, and in both groups this variable was significantly related to familial aggregation. When, for this reason, we matched probands by age-at-onset, the difference in survival from AD between relatives of C-AD and NH-AD groups was virtually completely eliminated. The results suggest that while C-AD samples draw very heavily from the left, i.e. early-onset, side of the distribution of AD probands, there is no discernable bias for probands with relatively strong familial factors *within* that part of the distribution. The development of AD at a relatively early age appears to be a sufficient incentive to actively seek treatment and we found no evidence that a positive family history adds to it.

With regard to the strong negative association between age at onset and familial aggregation, it is interesting to note that many early studies of C-AD probands, using the conventional, but arbitrary cut off ages of 60 and 65, failed to find differences in familial risk of AD when probands were dichotomized by onset age (Lautenschlager *et al.*, 1996; Li *et al.*, 1991, 1995). For reasons that are still unclear, however, these ages appear to be among the weakest points to divide probands in order to distinguish those with greater and lesser familial aggregation (Lautenschlager *et al.*, 1996; Li *et al.*, 1995). Several recent studies have approached the investigation of familial aggregation and onset in AD using a variety of alternative and more powerful strategies and have found familial aggregation strongly associated with earlier onset AD (Heun and Maier, 1995; Lautenschlager *et al.*, 1996; Li *et al.*, 1995; Silverman *et al.*, 1994a; Wu *et al.*, 1998). In part, this may be due to the influence of APOE- $\epsilon$ 4 leading to earlier expression of AD (Blackner *et al.*, 1997; Saunders *et al.*, 1993). In this regard, it is of interest that the frequency of the apolipoprotein E (APOE)  $\epsilon$ 4 allele appears to be strongly increased in a clinic-based versus community-based population of AD (Tsuang *et al.*, 1996). Interestingly, and analogous to what we found with age at onset in our study, these investigators found the difference in APOE allele frequencies between the two groups was eliminated after controlling for age at onset. In addition to APOE- $\epsilon$ 4, however, there is evidence that other, as yet unidentified, genes also

increase the risk of AD (Li *et al.*, 1996) and likely have age dependent expression (Silverman *et al.*, 1994a). Yet, genetic epidemiological data suggests that the increased risk associated with a biological relationship with an AD proband is strongest at relatively early onset ages and diminishes markedly by the ages when incidence of AD peaks in the ninth decade (Heun and Maier, 1995; Silverman *et al.*, 1994a).

The two NH-AD proband subgroups (diagnosed either by NINCDS or ICD-9) were demographically similar and, in survival analysis comparisons, showed highly similar levels of familial aggregation. The lack of full diagnostic uniformity, however, remains a weakness of the study and one which might have been more problematic if differences in familial aggregation between the C-AD and NH-AD groups had been observed even after controlling for age at onset. Had this been so, these differences might have arisen from reduced diagnostic accuracy in the NH-AD sample. Instead, however, the strong similarity observed between groups after matching by proband age at onset suggests that neither the differences in diagnostic assessment nor the differences in the source of ascertainment lead to differences in familial aggregation that cannot be explained by age at onset. Finally, had we only used either of the two NH-AD subgroups alone the results would have been essentially the same.

Our findings are relevant to physicians and clinical geneticists who provide counseling to non-demented patients concerned about their own risk of AD because of a parent or sibling with the disease. Depending on the onset characteristics of the relatives in question, the reliance on most available studies of familial aggregation may lead to a substantial overestimate of the risk. More generally, the present results underscore the inappropriateness of using any single estimate of the age-dependent risk of AD (survival curve) to characterize the risk of AD to relatives of AD probands. Onset age is a key factor associated with risk to relatives and a later onset in an AD proband suggests a lower risk to their first degree relatives compared to those related to probands with an earlier onset. It has long been established that the relatives of AD probands with a relatively early onset possess an increased risk for AD themselves, but it remains unclear just how familial is very late-onset (e.g., onset  $\geq 85$  years) AD. The present study suggests that that question can be pursued through pooling clinic- and nursing home-based

samples while making onset age distinctions and examining levels of familial aggregation.

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## REFERENCES

- Blackler D, Haines JL, Terwedow H, Go RCP, Harrell LE, Perry RT, Bassett SS, Chase GA, Meyers D, Albert MS, Tanzi R. 1997. ApoE-4 and age at onset of Alzheimer's disease. *Neurology* **48**: 139–147.
- Breitner JCS, Folstein MF. 1984. Familial Alzheimer's disease: a prevalent disorder with specific clinical features. *Psychol. Med.* **14**: 63–80.
- Brodaty H, Howarth GC, Mant A, Kurrle SE. 1994. General practice and dementia. A national survey of Australian GPs. *Med. J. Aust.* **160**: 10–14.
- Farrer LA, Cupples LA, van Duijn CM, Kurz A, Zimmer R, Muller U, Green RC, Clarke V, Shoffner J, Wallace DC, Chui H, Flanagan SD, Duara R, St. George-Hyslop PH, Auerbach SA, Volicer L, Wells JM, Van Broeckhoven C, Growden JH, Haines JL. 1995. Apolipoprotein E genotype in patients with Alzheimer's disease: implications for the risk of dementia among relatives. *Ann. Neurol.* **38**: 797–808.
- Hebert LE, Scherr PA, Beckett LA, Albert MS, Pilgrim DM, Chown MJ, Funkenstein HH, Evans DA. 1995. Age-specific incidence of Alzheimer's disease in a community population. *JAMA* **273**: 1354–1359.
- Heun R, Maier W. 1995. Risk of Alzheimer's disease in first degree relatives. *Arch. Gen. Psychiat.* **52**: 317–318.
- Kawas C, Segal J, Stewart WF, Corrado M, Thal L. 1994. A validation study of the Dementia Questionnaire. *Arch. Neurol.* **51**: 901–906.
- Klein JP, Moeschberger ML. 1997. *Survival Analysis: Techniques for Censored and Truncated Data*. Springer-Verlag: New York.
- Lautenschlager NT, Cupples LA, Rao VS, Auerbach SA, Becker R, Burke J, Chui H, Duara R, Foley EJ, Glatt SL, Green RC, Jones R, Karlinsky H, Kukull WA, Kurz A, Larson EB, Martelli K, Sadovnick AD, Volicer L, Waring SC, Growdon JH, Farrer LA. 1996. Risk of dementia of Alzheimer's disease patients in the MIRAGE study: what is in store for the oldest old? *Neurology* **46**: 641–650.
- Levy-Lehad E, Wijsman EM, Nemens E, Anderson L, Goddard KA, Webber JL, Bird TD, Schellenberg GD. 1995. A familial Alzheimer's disease locus on chromosome 1. *Science* **269**: 970–973.

- Li G, Silverman JM, Mohs RC. 1991. Clinical genetic studies of Alzheimer's disease. *Psychiat. Clin. N. Am.* **14**: 267–285.
- Li G, Silverman JM, Smith CJ, Zaccario ML, Schmeidler J, Mohs RC, Davis KL. 1995. Age at onset and familial risk in Alzheimer's disease. *Am. J. Psychiat.* **152**: 424–430.
- Li G, Silverman JM, Altstiel LD, Haroutunian V, Perl D, Purohit D, Burstein S, Lantz M, Mohs RC, Davis KL. 1996. Apolipoprotein e4 allele and familial risk in Alzheimer's disease. *Genet. Epidemiol.* **13**: 285–298.
- Li G, Aryan M, Silverman JM, Haroutunian VH, Perl DP, Lantz M, Marin D, Mohs RC, Davis KL. 1997. A validity study of family history assessment of primary progressive dementia. *Arch. Neurol.* **54**: 634–640.
- Mayeux R, Sano M, Chen J, Tatemichi T, Stern Y. 1991. Risk of dementia in first degree relatives of patients with Alzheimer's disease and related disorders. *Arch. Neurol.* **48**: 268–273.
- McKhann G, Drachman D, Folstein MF, Katzman R, Price D, Stadlen E. 1984. Report of the NINCDS-ADRDA work group under the auspices of the Department of Health and Human Services Task Force on Alzheimer's Disease. *Neurology* **34**: 939–944.
- Saunders AM, Strittmatter WJ, Schmechel D, St George-Hyslop PH, Pericak-Vance MA, Joo SH, Rosi BA, Gusella JF, Crapper-MacLachlan DR, Albert MJ, Hulette C, Crain B, Goldgaber D, Roses AD. 1993. Association of apolipoprotein E allele e4 with late-onset familial and sporadic Alzheimer's disease. *Neurology* **43**: 1467–1472.
- Silverman JM, Breitner JCS, Mohs RC, Davis KL. 1986. Reliability of the family history method in genetic studies of Alzheimer's disease and related dementias. *Am. J. Psychiat.* **143**: 1279–1282.
- Silverman JM, Keefe RSE, Mohs RC, Davis KL. 1990. A study of the reliability of the family history method in genetic studies of Alzheimer's disease. *Alzheimer's Disease Assoc. Disord.* **3**: 218–223.
- Silverman JM, Li G, Zaccario ML, Smith CJ, Schmeidler J, Mohs RC, Davis KL. 1994a. Patterns of risk in first-degree relatives of patients with Alzheimer's disease. *Arch. Gen. Psychiat.* **51**: 577–586.
- Silverman JM, Raiford K, Edland S, Fillenbaum G, Morris JC, Clark CM, Kukull W, Heyman A. 1994b. The Consortium to Establish a Registry for Alzheimer's Disease (CERAD), part VI: family history assessment: a multicenter study of first degree relatives of Alzheimer's disease probands and nondemented spouse controls. *Neurology* **44**: 1253–1259.
- Tanzi RE, Gaston S, Bush A, Ramano D, Pettingell W, Peppercorn J, Paradis M, Gurubhagavatula S, Jenkins B, Wasco W. 1993. Genetic heterogeneity of gene defects responsible for familial Alzheimer's disease. *Genetica* **91**: 255–263.
- Tsuang D, Kukull WA, Sheppard L, Barnhart RL, Peskind ER, Schellenberg GD, Raskind MA, Larson EB. 1996. Impact of sample selection on APOE  $\epsilon$  allele frequency: a comparison of two Alzheimer's disease samples. *J. Am. Geriatr. Soc.* **44**: 740–707.
- Wu Z, Kinslow C, Pettigrew KD, Rapoport SI, Schapiro MB. 1998. Role of familial factors in late-onset Alzheimer disease as a function of age. *Alzheimer Dis. Assoc. Disord.* **12**: 190–197.