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Increased Longevity in Offspring of Mothers With Alzheimer's Disease

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Abstract

Life expectancy is a familial trait. However, the effectiveness of using the age at death of a deceased parent to estimate life expectancy in their offspring can vary depending on whether death in the parent was due to extrinsic versus intrinsic causes, as well as demographic characteristics such as sex. While Alzheimer's disease (AD) risk increases with increased age, mortality for individuals with AD is increased in contrast to comparably aged individuals without AD. Yet in most cases it is not the defining neuropathology of AD that directly terminates life but instead conditions and illnesses extrinsic to AD pathology that nevertheless have increased likelihood in its presence. For this reason, we hypothesized that offspring of AD mothers would have greater longevity than offspring of mothers without AD (insufficient numbers prevented a comparable analysis using fathers with AD). The longevity of 345 offspring of 100 deceased 60+ year old AD mothers was compared with 5,465 offspring in 1,312 deceased 60+ year old non-AD mothers. We used a proportional hazards model that accounted for clustered (nonindependent) observations due to the inclusion of several offspring from the same family. In both an unadjusted model and one that adjusted for the age at death in the mother, and the sex and birth year in the offspring we found evidence for increased longevity in the offspring of AD mothers. The results suggest that, in addition to genes that might directly affect pathways leading to AD, there may be familial/genetic factors not connected to specific pathophysiological processes in AD but instead associated with increased longevity that contribute to the familial aggregation observed in AD.

Keywords

Alzheimer's disease; longevity; familiarity; life expectancy; genetics

INTRODUCTION

Life expectancy, the number of years an individual can expect to live, runs in families. While much of its variability remains unexplained by family history and genetics, knowing the length of someone's lifespan helps predict life expectancy in his or her close biological relatives [Korpelainen, 1999, 2000; Cournil and Kirkwood, 2001; Kemkes-Grottenthaler, 2004]. The predictive value of using age at death in one individual to estimate life expectancy in his or her relatives, however, can be affected by the whether the death in the deceased index family member was due to extrinsic or intrinsic causes. If "Jane" died as a passenger in a plane crash at 68 years of age, for example, then her lifespan can be considered extrinsically foreshortened. Jane's age at death, resulting from a cause that is

extrinsic to her biological/genetic makeup, still provides information for prediction relevant to her relatives (i.e., she lived as long as age 68 years). However, if this last environmental contingency—clearly unrelated to genetic and other pertinent familially shared factors—had not occurred, Jane would have lived beyond that age to some later, but unknown point. The later age would probably be a more useful predictor for her offspring. Using Jane's true, but foreshortened age at death would tend to underestimate the life expectancy in her relatives. If Jane instead died from heart disease or another intrinsic cause involving endogenous factors, then her age at death would probably better reflect shared familial/genetic frailties and related factors useful for estimating life expectancy in her close biological relatives.

A major risk factor for Alzheimer's disease (AD) is advanced age and, from the early 60s to at least the late 80s, the incidence of AD doubles about every 5 years [Jorm and Jolley, 1998]. Familial/genetic factors have a consistently demonstrated effect with respect to the risk of AD itself [Hendrie, 1998], although this role is complex, variable, and appears to diminish with age [Lautenschlager et al., 1996; Hendrie, 1998; Green et al., 2002; Silverman et al., 2005]. The relationship between AD in a given family member and the life expectancy of his or her biological relatives, however, has very rarely been investigated, with little or no apparent evidence to suggest an association with familial life expectancy [Heun and Bonsignore, 2004]. Nevertheless, there is a basis to suspect that relatives of a deceased individual may differ in their longevity depending on whether the individual had AD or not. Although longevity is reduced for people with AD when compared to similarly aged people without it [Wolfson et al., 2001; Larson et al., 2004], the neuropathologic changes in the brain that arise with AD do not usually directly terminate life [Beard et al., 1996]. The increased mortality in AD frequently can be attributed to the incidence of conditions that often have an etiology not owing directly to AD pathology. Instead, these conditions (e.g., pneumonia) tend to be more likely to arise when AD is present but they are secondary to AD and not an intrinsic part of the disease itself. Other factors being equal, the lifespan of an individual with AD may be more prone to foreshortening due to extrinsic causes compared with someone without AD. If so, using the age at death of someone with AD may tend to underestimate the life expectancy of their relatives. Based on these considerations, we hypothesized that longevity will be greater in the offspring of a deceased parent with AD compared with the offspring of a deceased parent without AD after making appropriate adjustments for key factors affecting longevity such as the age at death of the parent and the offspring's own sex and secular effects related to a given birth cohort.

METHODS

Ascertainment of Families

The families in this study were all originally ascertained through living nondemented elderly individuals (NDEIs) aged 60 or older. The NDEIs were required to be functional in the community (although physical impairments might be present), to have no subjective memory complaints, and to be able to provide comprehensive detailed histories regarding themselves, their family of origin, and their spouse (if married). A detailed description of the recruitment and diagnostic procedures has been described elsewhere [Silverman et al., 1994, 2003, 2005]. Briefly, since 1984, the Family Studies Research Center based at Mount Sinai Medical Center in Manhattan and the Veteran's Affairs Medical Center (VA) in the Bronx has collected detailed data pertaining to the first degree family members of NDEIs using uniform procedures in interviews either directly conducted or supervised by JMS. These NDEIs have been recruited through spouses of AD probands ascertained at our Alzheimer's Disease Research Center (ADRC), nondemented permanent and temporary (i.e., rehabilitation) residents at the Jewish Home and Hospital (JHH), and assisted living facility, Kittay House, associated with the JHH, and community dwelling individuals recruited through senior centers for well elderly, mailings, and outpatient health care facilities and

clinics unrelated to memory or other cognitive functions located in the New York metropolitan region.

Having first ascertained these families through a living NDEI, we classified the families on the basis of the AD/dementia status of the NDEI's mother or, independently, the father. The heritability of the life expectancy of offspring for both sexes has been observed in several studies to be stronger when the mother's lifespan is used versus the father's [Korpelainen, 1999, 2000; Kemkes-Grottenthaler, 2004]. For that reason and also owing to the greater life expectancy in women, we considered mothers with and without AD separately from fathers and we restricted families to those where the given parent of interest lived at least to age 60 and so lived to face at least some level of risk for AD. We then assessed longevity in the offspring of these two groups.

For this study it was an advantage that almost all of the parents of the NDEI series were deceased at the time of assessment as this allowed their full lifespan to be included as a covariate in our analyses when we examined the additional effect of AD in the parent. In this regard we note that although we have concurrently collected family histories on large numbers of AD probands [Silverman et al., 2005], these probands would not have been appropriate to use since they were almost always still alive at the time of their assessment and, hence, we did not know the extent of their full lifespan. Finally, we excluded families where the parent of interest was given a dementia diagnosis other than AD or the dementia status could not be determined.

There were 1,484 families of NDEIs with mothers who had lived 60+ years. Of these 29 families were excluded because the mother was given a dementia diagnosis other than AD and 43 additional families were excluded because the mother was still alive at assessment time (all nondemented). Thus, with respect to mothers, there were 1,412 families who met the full eligibility criteria. Of these mothers, 1,312 were classified as not demented up through the time of their death, and 100 were classified as having AD.

There were 1,342 families of NDEIs with fathers who had lived to 60+ years. Of these, 7 fathers were given a dementia diagnosis other than AD and 14 fathers were still alive at the time of assessment (1 with AD, 13 nondemented). However, probably both because men die at earlier ages [Austad, 2006] and have a reduced risk of AD compared with women [McDowell, 2001], only 32 fathers were diagnosed with AD. This number was too small to meaningfully analyze longevity in their offspring of fathers with AD. Thus, longevity in offspring was examined only on the basis of the mother's AD status.

Assessment of Relatives

The siblings and parents of the nondemented elderly were identified in telephone or in-person with one or more family informants. The Alzheimer's Disease Risk Questionnaire (ADRQ) [Breitner and Folstein, 1984] was used to assess birth year, sex, current age (if alive), or age at and cause of death (if not) for each relative [Silverman et al., 1986]. The ADRQ was also used to screen for dementia, cognitive impairment, or memory loss of any type and, if one or more of these was suggested for a given relative, the Dementia Questionnaire (DQ) [Silverman et al., 1989] was administered. The 50 item DQ is used to determine whether a dementia was present and, if so, its specific type. Using the information collected with these instruments, AD in parent and offspring was diagnosed according to previously published criteria [Silverman et al., 1989] similar to DSM-IV for dementia of the Alzheimer's type [American Psychiatric Association, 1994] but modified for informant-based assessment. This method has very good inter-informant [Silverman et al., 1986] and test-retest [Silverman et al., 1989] reliability. Furthermore, in both our own hands and others, the DQ has shown excellent sensitivity and specificity for identifying dementias

ascertained through direct clinical and neuropathological diagnoses [Kawas et al., 1994; Li et al., 1997; Ellis et al., 1998]. All protocols used were approved by the Institutional Review Boards at Mount Sinai, the Bronx VA, and the JHH and informed consent was obtained from NDEIs/informants. Also, an IRB waiver of informed consent was obtained on those relatives assessed through informant interviews.

Statistics

The Cox proportional hazards model was used to compare longevity in the offspring of mothers with AD with the offspring of mothers without AD [Klein and Moeschberger, 1997]. We used the S-Plus version 7.0 implementation of the Cox Model [Insightful Corporation, 2005]. Since all the offspring in a given family were included, members of the same sibship created clusters in which biodemographic data is not independently observed, the random effect variable “family” was included as clustering factor in all models examined. We first examined an unadjusted model in which, beyond “family,” longevity differences associated only with the dementia status of the mother would be examined. Second, we examined an adjusted model in which useful and potentially confounding predictors of longevity would also be included. We identified several potential covariates that would be included first in the model if we found they had significant associations with the dependent variable, longevity in the offspring. First, it is well established that there are sex differences in longevity and thus the sex of the offspring would likely be an important covariate. Second, we examined whether each parent type’s lifespan was related to the longevity in the offspring. Third, given that there are secular changes associated with lifespan [Kinsella and Velkoff, 2002], the year of birth of the offspring was considered for inclusion in the model. The Cox model is a semi-parametric model that makes no assumptions about the shape of the hazard rate but does assume that it remains proportional as the predictors vary. Thus, this proportionality assumption was assessed for each predictor in the model to see if the relationship between the hazard rate and each covariate remained proportion or instead varied as function of time.

RESULTS

Table I shows the demographic characteristics of the mother’s and their offspring in the two groups. The average age at death among mothers with AD was significantly greater than the age at death of the mothers without AD ($t = -6.91$, $df = 1410$, $P < 0.001$). This was expected since AD is a disorder of old age and its risk increases substantially as age increases. Thus AD will be disproportionately found among longer lived individuals. However the large size of the non-AD mother sample ensured that there were many non-AD mothers who lived to those same late ages as well. For example, there were 230 non-AD mothers who lived beyond age 90 so that adequate numbers were available to meaningfully covary for the mother’s age at death up through very late ages. The mean age at AD onset in the AD mothers group was 81 (± 8) years. There were no significant differences in the age at death of the father or the ages and proportion of women among the offspring. The crude proportion of deaths (i.e., no age correction applied) was significantly different between the two groups but the age at death in those offspring that had died was not significantly different.

For each possible predictor we assessed whether the proportionality assumption held and found no violations, that is, the hazard rate showed no evidence of varying across time for any of the predictors. Using “family” as clustering factor but unadjusted for any covariates, the presence of AD in the mother was significantly associated with increased longevity in the offspring ($z = -3.22$, $P = 0.001$). The mortality hazard ratio associated with being an offspring of an AD mother was 0.75 (95% confidence interval [CI]: 0.62, 0.89), reflecting a 25% better rate of survival than the offspring of mothers without AD.

As expected, there were significant effects of offspring's sex, offspring's birth year, and mother's age at death. We also looked at father's age at death but did not find a significant effect ($z = -1.56$, n.s.). With the family clustering variable included and controlling all the significant covariates, we again tested mother's AD status and found it to be positively associated with offspring longevity ($z = -2.05$, $P < 0.05$). The adjusted mortality hazard ratio associated with being an offspring of a mother with AD was 0.83 (95% CI: 0.694, 0.991) reflecting a 17% better rate of survival in these offspring independent of offspring sex, offspring birth year, and the age at death of the offspring's mother. Figure 1 shows the survival function estimate across the lifespan using the adjusted model. The overall mean values were used for birth year and mother's age at death and four separate lines were made using the coefficient values for male and female offspring and for mothers with and without AD.

DISCUSSION

In an unadjusted model and also after controlling for sex, year of birth, and the age of the mother's death, we found support for the hypothesis that the rate of longevity is significantly better among the offspring of mothers who had AD compared with the offspring of mothers who were not demented.

The genetic causes of AD in rare early onset cases (e.g., presenilin 1, presenilin 2, amyloid precursor protein) and the genetic risk factors in more common later onset cases (e.g., apolipoprotein E) that have so far been identified uncontroversially help to explain the increased familial aggregation of AD [Rocchi et al., 2003]. In addition, there are very likely other genetic factors, still to be identified, that directly effect the pathophysiological processes leading to AD [Farrer et al., 1995; Li et al., 1996; Rocchi et al., 2003]. However, especially since the risk of AD is so strongly associated with advancing age, the results of this study suggest that some additional portion of the increased rates of illness observed in this group might be unrelated to genes specifically involved in these pathways, but instead are familial/genetic factors attributable to greater longevity in this group. In other words, some genes that may be observed to be associated with AD may be those involved in longevity. In such genes, the specific alleles found more commonly among AD cases may well be unrelated to the pathophysiology of AD but rather to processes that promote a longer life.

We are aware of only one other study that examined familial longevity and AD. In apparent contrast to our study, no differences in longevity between the first degree relatives of AD probands and those of nondemented age-matched controls were observed [Heun and Bonsignore, 2004]. However, while the ages of the AD and index controls (NDEIs) were comparable, it is important to note that the AD and NDEI index subjects were still alive at the time of the study. Since AD increases mortality, the life expectancy in the comparably aged NDEIs would likely be greater than for the AD probands. Given the familiarity of life expectancy, this would make any increased longevity among relatives of AD probands hard to detect through comparisons with the relatives of these likely longer living NDEIs. Indeed, if AD *did not* positively influence life expectancy in first degree relatives, the longevity of the relatives of AD probands could be expected to be *less* than the relatives of the NDEIs. Thus, perhaps paradoxically, one could argue, albeit tentatively, that the earlier study's failure to find differences in longevity between the two groups of relatives examined, as opposed to decreased longevity in the relatives of the AD probands, might be seen as consistent with relatively increased familial longevity associated with AD and thus also with the findings in the present study.

Note that, in the present study, the living index subjects used to assemble a large group of families were *all* NDEIs; we did not use the living index subjects to categorize the families into AD and nondemented groups. The categorization of the families in AD and nondemented groups was instead made through the status of the deceased mothers of the NDEIs, some of whom had AD and some of whom did not have dementia.

Certain other methodological issues require discussion. First, the average AD onset age in the mothers with AD in our sample was 81 years, and only 21% of the sample had an onset prior to age 75. Thus, the observed association between AD in mothers and longevity in their offspring might be restricted to such later onset cases of AD. Second, the requirement that family eligibility depended on the mother being deceased could have biased our samples toward families with reduced familial longevity. This would be problematic if a substantial number of elderly mothers were still alive. But in fact, only 43 families of the original 1,477 were excluded on this basis, less than 3% of the original sample. Third, it remains an unanswered question whether there is a comparable effect on longevity associated with the AD status of an individual's father because we lacked sufficient numbers of fathers with AD to test this. Fourth, we did not find a significant association between the father's age at death and longevity in his offspring. This is consistent with several studies suggest that a paternal contribution to offspring lifespan is weaker than a maternal contribution [Korpelainen, 1999, 2000; Kemkes-Grottenthaler, 2004].

If, as seen here, relatives of AD probands tend to live longer than relatives of comparably aged control probands then this has methodological relevance for familial aggregation studies of AD. Without appropriate corrections included, survival analytic studies of families of AD and controls rely on the assumption of comparable censoring rates. If, instead, the outcome of interest is associated with censoring, then the results obtained will be biased. Our results suggest that survival analytic studies in which AD is the outcome will tend to be biased toward higher rates of AD in relatives of AD probands versus nondemented controls owing in part to a decreased probability of censoring in that group arising from their increased longevity. As already discussed, any increased familial aggregation observed that is attributable to this specific bias may yet reveal something important about genetic factors in AD—an association between increased familial longevity and AD.

REFERENCES

- American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 4th edn.. Washington: American Psychiatric Association; 1994.
- Austad SN. Why women live longer than men: Sex differences in longevity. *Gen Med*. 2006; 3(2):79–92.
- Beard CM, Kokmen E, Sigler C, Smith GE, Petterson T, O'Brien PC. Cause of death in Alzheimer's disease. *Ann Epidemiol*. 1996; 6(3):195–200. [PubMed: 8827154]
- Breitner JCS, Folstein MF. Familial Alzheimer's disease: A prevalent disorder with specific clinical features. *Psychol Med*. 1984; 14:63–80. [PubMed: 6200894]
- Cournil A, Kirkwood TB. If you would live long, choose your parents well. *Trends Genet*. 2001; 17(5):233–235. [PubMed: 11335017]
- Ellis RJ, Jan K, Kawas C, et al. Diagnostic validity of the dementia questionnaire for Alzheimer disease. *Arch Neurol*. 1998; 55(3):360–365. [PubMed: 9520010]
- Farrer LA, Cupples LA, van Duijn CM, et al. Apolipoprotein E genotype in patients with Alzheimer's disease: Implications for the risk of dementia among relatives. *Ann Neurol*. 1995; 38:797–808. [PubMed: 7486872]
- Green RC, Cupples LA, Go R, et al. Risk of dementia among white and African American relatives of patients with Alzheimer disease. *JAMA*. 2002; 287(3):329–336. [PubMed: 11790212]

- Hendrie HC. Epidemiology of dementia and Alzheimer's disease. *Am J Geriatr Psychiatry*. 1998; 6(2 Suppl 1):S3–S18. [PubMed: 9581216]
- Heun R, Bonsignore M. No evidence for a genetic relationship between Alzheimer's disease and longevity. *Dement Geriatr Cogn Disord*. 2004; 18(1):1–5. [PubMed: 15084787]
- Insightful Corporation. S-Plus 7 Function Guide. Seattle, Wa: Insightful Corporation; 2005.
- Jorm AF, Jolley D. The incidence of dementia: A meta-analysis. *Neurology*. 1998; 51(3):728–733. [PubMed: 9748017]
- Kawas C, Segal J, Stewart WF, Corrado M, Thal L. A validation study of the Dementia Questionnaire. *Arch Neurol*. 1994; 51:901–906. [PubMed: 8080390]
- Kemkes-Grottenthaler A. Parental effects on offspring longevity—Evidence from 17th to 19th century reproductive histories. *Ann Hum Biol*. 2004; 31(2):139–158. [PubMed: 15204358]
- Kinsella K, Velkoff VA. Life expectancy and changing mortality. *Aging Clin Exp Res*. 2002; 14(5): 322–332. [PubMed: 12602565]
- Klein, JP.; Moeschberger, ML. Survival analysis: Techniques for censored and truncated data. New York: Springer-Verlag; 1997.
- Korpelainen H. Genetic maternal effects on human life span through the inheritance of mitochondrial DNA. *Hum Hered*. 1999; 49(4):183–185. [PubMed: 10436377]
- Korpelainen H. Variation in the heritability and evolvability of human lifespan. *Naturwissenschaften*. 2000; 87(12):566–568. [PubMed: 11198201]
- Larson EB, Shadlen MF, Wang L, et al. Survival after initial diagnosis of Alzheimer disease. *Ann Intern Med*. 2004; 140(7):501–509. [PubMed: 15068977]
- Lautenschlager NT, Cupples LA, Rao VS, et al. Risk of dementia of Alzheimer's disease patients in the MIRAGE study: What is in store for the oldest old? *Neurology*. 1996; 46:641–650. [PubMed: 8618660]
- Li G, Silverman JM, Altstiel LD, et al. Apolipoprotein E-epsilon 4 allele and familial risk in Alzheimer's disease. *Genet Epidemiol*. 1996; 13(3):285–298. [PubMed: 8797010]
- Li G, Aryan M, Silverman JM, et al. The validity of the family history method for identifying Alzheimer disease. *Arch Neurol*. 1997; 54(5):634–640. [PubMed: 9152121]
- McDowell I. Alzheimer's disease: Insights from epidemiology. *Aging (Milano)*. 2001; 13(3):143–162. [PubMed: 11442298]
- Rocchi A, Pellegrini S, Siciliano G, Murri L. Causative and susceptibility genes for Alzheimer's disease: A review. *Brain Res Bull*. 2003; 61(1):1–24. [PubMed: 12788204]
- Silverman JM, Breitner JC, Mohs RC, Davis KL. Reliability of the family history method in genetic studies of Alzheimer's disease and related dementias. *Am J Psychiatry*. 1986; 143(10):1279–1282. [PubMed: 3766791]
- Silverman JM, Keefe RS, Mohs RC, Davis KL. A study of the reliability of the family history method in genetic studies of Alzheimer disease. *Alzheimer Dis Assoc Disord*. 1989; 3(4):218–223. [PubMed: 2597424]
- Silverman JM, Li G, Zaccario ML, et al. Patterns of risk in first-degree relatives of patients with Alzheimer's disease [see comments]. *Arch Gen Psychiatry*. 1994; 51(7):577–586. [PubMed: 8031231]
- Silverman JM, Smith CJ, Marin DB, Mohs RC, Propper CB. Familial patterns of risk in very late-onset Alzheimer disease. *Arch Gen Psychiatry*. 2003; 60(2):190–197. [PubMed: 12578437]
- Silverman JM, Ciresi G, Smith CJ, Marin DB, Schnaider-Beeri M. Variability of familial risk of Alzheimer disease across the late life span. *Arch Gen Psychiatry*. 2005; 62(5):565–573. [PubMed: 15867110]
- Wolfson C, Wolfson DB, Asgharian M, et al. A reevaluation of the duration of survival after the onset of dementia. *N Engl J Med*. 2001; 344(15):1111–1116. [PubMed: 11297701]

Fig. 1.
Survival curves based on Cox model including mother's AD status, mother's age at death, offspring's birth year and offspring's sex. Separate lines are given for male and female offspring of mother's with AD and mother's without AD.

TABLE I
Characteristics of Nondemented Families With Deceased Mothers Either Without Dementia or With AD

Group	# Families	Mother's age at death (SD) *	Father's age at death (SD)	All offspring				
				# Offspring	Age (SD)	# Female (%)	# Deceased (%)**	Age at death (SD)
Mother without AD	1,312	79 (10)	71 (16)	5,465	70 (18)	2,747 (50.3)	2,594 (47.6)	65 (22)
Mother with AD	100	86 (8)	72 (17)	345	72 (15)	181 (52.5)	123 (35.6)	67 (22)

* $t = -6.91$, $df = 1,410$, $P < 0.001$.

** Chi-square = 17.64, $df = 1$, $P = 0.0001$.