Heritability for Alzheimer’s Disease: The Study of Dementia in Swedish Twins

Margaret Gatz,1 Nancy L. Pedersen,1,2 Stig Berg,1,3 Boo Johansson,3 Kurt Johansson,4 James A. Mortimer,3 Samuel F. Posner,6 Matti Viitanen,4 Bengt Winblad,4 and Anders Ahlbom2

1Department of Psychology, University of Southern California, Los Angeles.
2Division of Genetic Epidemiology, Institute of Environmental Medicine, The Karolinska Institute, Stockholm, Sweden.
3Institute of Gerontology, University College of Health Sciences, Jonkoping, Sweden.
4Department of Clinical Neuroscience and Family Medicine, Division of Geriatric Medicine, Karolinska Institute, Huddinge University Hospital, Huddinge, Sweden.
5Institute on Aging, University of South Florida, Tampa.
6*Medical Effectiveness Research Center for Diverse Populations, University of California–San Francisco.

Background. Alzheimer’s disease has been thought to have familial and sporadic forms, and several genetic defects have been identified that chiefly explain early-onset familial cases. In this study, our purpose was to detect all cases of dementia in an established twin registry and to estimate total extent of genetic contribution to liability to Alzheimer’s disease.

Methods. At the first stage, members of the registry were screened for dementia, using in-person or telephone mental status testing. At the second stage, those who screened positively and their partners were referred for clinical work-ups, including neuropsychological assessment, physician examination, laboratory tests, and neuroimaging. Clinical diagnoses were assigned at a multidisciplinary consensus conference. Probandwise concordance rates were examined by zygosity, and structural modeling was applied to the data to estimate genetic and environmental influences, using both single- and multiple-threshold models.

Results. Sixty-five pairs were identified in which one or both was demented. The probandwise concordance rate for Alzheimer’s disease among monozygotic pairs was 67%; the corresponding figure for dizygotic pairs was 22%. Heritability of liability to Alzheimer’s disease was estimated to be .74; to any dementia, .43. The other variance is attributable to environmental influences.

Conclusions. Findings indicate a substantial genetic effect for these predominantly late-onset Alzheimer’s disease cases. At the same time, structural modeling results and large intra-pair differences in age of onset suggest that environmental factors are also important in determining whether and when an individual may develop dementia.
mal aging, thereby providing a sample that is derived from a population and is not restricted by age or gender, nor limited to institutionalized cases or to those who have sought medical treatment.

METHODS

Sample

The Study of Dementia in Swedish Twins is based on the Swedish Adoption/Twin Study of Aging, or SATSA (12). SATSA consists of a subset of twins from the population-based Swedish Twin Registry (13). SATSA includes all 961 pairs from the twin registry who indicated having been reared apart and a matched sample of 961 pairs who were reared together, drawn from the twin registry to correspond in sex, year of birth, and county of birth to the reared-apart twins (14). Members of the SATSA panel have been surveyed every three years, while a subset of complete pairs aged 50 and older has participated in in-person cognitive and health assessments on a three-year rolling schedule.

For purposes of the dementia study, all twins identified for the SATSA sample were included, whether or not they had responded to SATSA data collection efforts. Due to very low prevalence of dementia shown in population surveys among those under age 55 (15), only pairs born in 1935 or previously, of whom one or both twin partners was alive in 1987, were included in the dementia study. The resulting base sample consisted of 781 pairs plus 416 surviving partners aged 55 and older (1978 individuals altogether). Across all individuals, 33.9% were monozygotic (MZ), while 35.0% of the complete pairs were MZ, figures that correspond to the registry as a whole. Zygosity was initially determined by questionnaire and then confirmed serologically. All pairs are of the same sex.

Screening Procedures

Case ascertainment entailed, first, screening all pairs in the SATSA sample to establish whether or not the person should be regarded as a suspected proband for dementia, and second, conducting a diagnostic assessment of each suspected case. Subjects and collaterals were informed about the study in accordance with the Ethics Committee of the Karolinska Institute and the Swedish Data Inspection Board.

Screening took advantage of the level of data available from SATSA: participation in mailed surveys and in-person assessment; surveys only; or nonrespondent to surveys. Figure 1 shows these different pathways. Those who had requested to be removed from future twin studies (n = 194) were not screened, leaving a sample of 1,784.

For 638 individuals, in-person cognitive testing results were available, including the Mini-Mental State Examination [MMSE; (16)]. The MMSE was modified to include

<table>
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<th>Pathway</th>
<th>Cases Excluded</th>
<th>Cases Rescreened</th>
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<td>178</td>
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Figure 1. Flow chart indicating case ascertainment methods, response rates, and outcomes.
recognition questions if recall questions were missed; each of these three items earned half credit. Therefore, a cutoff score of 24.5 was used.

Another 466 individuals responded to the most recent SATSA survey but were not participants in the in-person testing. Individuals who returned the survey were regarded as intact unless identified through one of two secondary methods: registry linkage (described below) or a family member’s contacting us by telephone or by letter to indicate that this member of the SATSA sample was having cognitive difficulty. Altogether, 48 individuals were identified through reports of family members.

For the remaining SATSA survey nonresponders, screening was by means of a telephone interview [TELE; (17)]. Telephone numbers were obtained by submitting the names to a national listing of telephone numbers. Before they could be screened, 89 of the survey nonresponders had died. Another 86 were unable to be reached, because they had emigrated or had unlisted telephone numbers or were not locatable through the telephone listing or never answered. Of the 457 who were reached, 317 agreed to an interview and 140 refused. Altogether, evaluation with either the MMSE or TELE was achieved with 80.9% of those slated for screening and still alive.

The telephone interview incorporated the Mental Status Questionnaire [MSQ; (18)]; items to tap other cognitive domains, i.e., attention and working memory, short-term memory, and cognitive abstraction; and questions about health and functional status, self-reported memory functioning, and depression. A proxy form of the interview focused on functional status, memory functioning, and depression, including history and course of any cognitive or memory problems.

Finally, registry linkage was employed in which all members of the SATSA sample were matched with the Swedish Psychiatric In-patient Registry in order to identify any member of the SATSA sample with any diagnosis of dementia. Registry linkage offers the advantage that all individuals are screened regardless of their participation status in SATSA. However, in part because records were available only for 1972–1983, this method of screening was essentially infrequent, resulting in only 4 matches.

Evaluations of Screening Methodology

Two issues were of concern. First, we wished to identify all potential cases and to avoid false negatives. Second, we wished to avoid any bias in screening with respect to zygosity. Therefore, we undertook several ancillary analyses to evaluate the screening methodology.

The assumption that those able to answer the survey completely without assistance were nondemented was tested through applying the telephone protocol to a sample of survey responders. A sample of 70 was identified, of whom one refused and 69 were interviewed. None was determined to be demented.

The sensitivity and specificity of the telephone interview were tested on an established registry of 41 Alzheimer’s disease patients and controls. In this selected sample, response rate was 90%, sensitivity was 100%, and specificity was 91% (17).

In completed diagnostic workups with suspected probands in the present study, the false positive rate was 33.6%. Thus, there is considerable loss of specificity in an unselected population. Of 32 partners who screened negative, 31 were not demented and one was a false negative. Apart from partners, we have no basis on which to estimate a false negative rate. However, our design has built into it the feature that everyone is rescreened at 3-year intervals. We now have six examples of cases who were negative at screening but subsequently found to be demented. None had an age of onset earlier than the screening, confirming that the screening result was correct.

Thus, with multiple ways of entering the study, we enhanced our chances of including all cases of dementia. Particularly notable is that considerable effort was put into screening those who were nonresponders in the longitudinal panel, and that over 40% of those who screened positive came from this group. To the extent that under-ascertainment did occur, there is no reason to believe that it was biased. At all stages, personnel collecting data were blind to zygosity. Nearly the same proportions of MZ and dizygotic (DZ) twins were screened by each method. Among those who screened positive, 34.1% were monozygotic, matching the distribution of zygozy in the base population.

Determination of Diagnoses

The diagnostic evaluation employed a nurse, psychologist, and physician trained in geriatric medicine. The protocol parallels Consortium to Establish a Registry for Alzheimer’s Disease (CERAD) procedures for physical and neurological evaluations, laboratory tests, neuropsychological testing, and neuroimaging (19). Evaluation was discontinued and the suspected proband excluded if it was learned during the evaluation that the individual was not demented but instead had some other condition, such as psychiatric disorder or mental retardation.

After workups were complete, findings were presented at a consensus diagnosis conference, where the chair (BJ) was blind to zygosity and to any information other than that presented at the conference. Each professional presented her or his independent opinion, and the final diagnosis was reached through discussion. Diagnostic decisions were guided by checklists that correspond to DSM-III-R criteria for dementia (20) and for level (severity) of dementia, NINCDS/ADRDA criteria for probable and possible Alzheimer’s disease (21), and — once available — NINDS-AIREN criteria for vascular dementia (22).

Twin partners of probands were given an identical clinical workup. While probands were all alive at the time of screening, partners were brought into the study regardless of their status in 1987. Among co-twins of probands, 53% of MZ and 55% of DZ were still living. If the partners were deceased and therefore had not been screened, their diagnostic assessment included informant interviews (23) and review of medical records, including death certificates. Analyses were subsequently conducted in two ways, both including all pairs and excluding pairs where the partner died prior to the age of onset of the proband (i.e., “truncated pairs”).

Mean age at workup was 78.4 years ($SD = 7.9$) for MZ.
and 77.5 years (SD = 7.8) for DZ twins. Age of onset was established by asking the informant for a description of memory and other problems, followed by the age at which these changes were observed (24). Where medical records were available, they were used to crosscheck the information.

Cases and partners are being followed longitudinally every 18 months, with post-mortem neuropathological examination for any who die. Diagnoses used in the analyses reported here reflect longitudinal clarification but not new cases of dementia. One case that had been classified as ‘other dementia’ met criteria for possible Alzheimer’s disease longitudinally; two cases that had been called Alzheimer’s disease were changed to reflect other dementia (in one instance, mixed Alzheimer’s and vascular dementia; in the other, dementia of ambiguous etiology).

Autopsy confirmation of diagnosis is available for 10 cases. There was concurrence on 9 cases between clinical diagnosis and neuropathological results (5 of these were Alzheimer’s disease cases). On the tenth, from a DZ pair, clinical diagnosis was vascular dementia, whereas neuropathology supported a diagnosis of Alzheimer’s disease.

**RESULTS**

**Sample Characteristics**

A total of 75 probands were identified: 38 probable Alzheimer’s disease, 11 possible Alzheimer’s disease, 12 vascular dementia, and 14 mixed or other dementia diagnoses. Among partners not primarily ascertained were 5 probable Alzheimer’s disease, 2 possible, 1 vascular dementia, and 4 with other dementia diagnoses. Sixty-five pairs were available for twin analyses, reflecting the fact that 7 pairs (3 MZ and 4 DZ) had been doubly ascertained; that is, both members of the pair screened positive and were diagnosed as demented; and 3 partners refused to participate in the assessment, losing those 3 pairs to analysis.

There was no significant difference by zygosity in age of onset. Among MZ pairs, mean age of onset for all Alzheimer’s disease cases was 75.8 years (SD = 9.03, range 60–91 years). Among DZ pairs, mean age of onset was 73.7 years (SD = 8.92, range 47–90 years).

**Prevalence Estimates**

The prevalence rate of dementia for those in the sample aged 65 and older and alive in 1987 was 4.9%, and the rate of Alzheimer’s disease was 3.3%. These calculations are based on a weighted combination of sample prevalences across subgroups defined by screening outcome, but without including any false negatives. These rates compare well to other diagnostic group for calculating separate concordance rates. However, there were no pairs concordant for vascular dementia. Concordance rates were then calculated for all dementias. Difference in concordance between MZ and DZ pairs was substantial but not statistically significant. The fact that the concordance rate for MZ pairs for all dementias was somewhat higher than for Alzheimer’s disease alone was due to three DZ pairs in which the proband had Alzheimer’s disease, while the partner had another dementia; there was only one such MZ pair.

**Concordance Rates**

The first step in twin analyses is computation of concordance rates in monozygotic and dizygotic twins. Concordance rates - a usual means of reporting results from twin studies of psychopathology — make use of the fact that MZ twin pairs are genetically identical whereas DZ twins share on average only half of their segregating genes. Probandwise concordance rates represent the ratio of the number of affected twin partners of independently ascertained probands to the total number of probands. If MZ twin pairs have a higher concordance rate than DZ twin pairs, the importance of genetic effects is indicated. For calculating probandwise concordance for Alzheimer’s disease, probands with definite, probable, or possible Alzheimer’s disease were included. Pairs were regarded as concordant if the partner had Alzheimer’s disease or mixed Alzheimer’s and vascular pathology or unspecified dementia. Pairs where the partner had vascular dementia or a dementia due to another specified cause (e.g., hydrocephalus, Parkinson’s disease) were excluded. Results shown in Table 1 indicate significantly greater probandwise concordance for Alzheimer’s disease for MZ than for DZ pairs. (For all pairs, difference between concordance rates = 44.8, 95% CI = .001, 80.8).

There were insufficient probands in any other diagnostic group for calculating separate concordance rates. However, there were no pairs concordant for vascular dementia. Concordance rates were then calculated for all dementias. Difference in concordance between MZ and DZ pairs was substantial but not statistically significant. The fact that the concordance rate for DZ pairs for all dementias was somewhat higher than for Alzheimer’s disease alone was due to three DZ pairs in which the proband had Alzheimer’s disease, while the partner had another dementia; there was only one such MZ pair.

**Tetrachoric Correlations**

Also shown in Table 1 are tetrachoric correlations, with 95% confidence intervals, for Alzheimer’s disease and for all dementias. Tetrachoric correlations, representing the correlation of liability between relatives, are calculated using PRELIS (25). The values are analogous to intraclass correlations based on continuous data. All pairs are used in which both members of the pair could be given a value of 1 (demented) or 0 (not demented). The 0 values were assigned to any individual who was determined not to be demented after clinical workup and to any individual whose screening outcome was negative. In these contingency tables, each pair is entered only once, even if doubly ascertained.

Results indicate a very high degree of twin similarity. MZ pairs are more similar than DZ pairs, pointing to substantial heritability. At the same time, MZ pairs appear to be less than twice as similar as DZ pairs. Therefore, not all of the similarity between pairs can be explained by genetic influences.

Tetrachoric correlations were also calculated for twins reared together and twins reared apart. Results for Alzheimer’s disease were .76 and .70, respectively. As these are not significantly different from one another, rearing status was not considered further.
Threshold Models

Recent analytical advances in twin methodology use structural model-fitting techniques in order to estimate genetic and environmental components of variance (26). These methods are based on liability-threshold models, which assume a latent, normally distributed liability to disease that is manifest as a categorical phenotype, i.e., demented or not demented (27). For dichotomous or ordinal data, models are fit to contingency tables for MZ and for DZ twins using the Mx program (28). A threshold is fixed at a z-score corresponding to prevalence of dementia in the sample. Heritability (h²) is an estimate of the relative importance of additive genetic differences for the variance in a population. Shared environment (c²) reflects experiences that contribute to twin similarity, e.g., living in a rural area. Non-shared environment (e²) refers to the contribution of environmental experiences not shared by twin pairs, e.g., different work histories. Expectations for fitting the observed data are based on the fact that genetic similarity is half as great for DZ as for MZ twin pairs, while shared environmental influences contribute equally to making MZ and DZ pairs similar. A series of models was tested, with all three parameters included in the full model, and then successively dropping either the h² or the c² parameter. Degrees of freedom reflect the number of parameters being estimated, the number of constraints, and the number of observed statistics. Indicators of fit include chi square and Akaike’s Information Criterion [AIC; (29)]. A significant increase in the chi square goodness-of-fit between the full and reduced model indicates that the reduced model fits the data less well than the full model. Final determination of which model to accept is based on a combination of statistical indicators, parsimony, genetic logic, and consistency with inferences based on the correlations and concordances.

Models were fit for Alzheimer’s disease and for all dementias. In addition, for all dementias, a multiple-threshold model was used with three levels: demented, mild cognitive impairment (insufficient for diagnosis as demented), and not demented. A multiple-threshold model is based on the assumption that the same underlying liability is reflected in dementia and in mild cognitive dysfunction. Power analyses have shown that low population prevalence diseases (i.e., a high threshold) require inordinately large sample sizes to have sufficient power for identifying accurate estimates for the components of variance (30). Multiple-threshold models generally afford some improved power. Still, because of the small sample sizes in the present study, standard errors are quite large.

Resulting parameter estimates from a series of models are shown in Table 2. The second and third models are each nested in the full model but not in each other. The full model appears to offer the best solution. Models that drop the additive genetic parameter have a poorer fit, meaning that this parameter must be retained. While h² and c² are difficult to distinguish in these models, the pattern of correlations argues for retaining the shared environmental parameter.

The multiple-threshold model gave a reasonable fit to the data, suggesting that there may be a shared liability underlying dementia and mild cognitive impairment, and that these represent a continuum of dysfunction. To date, just 10% of the mildly impaired individuals have gone on to develop dementia when followed up longitudinally.

Table 2 shows only the models with thresholds corresponding to the contingency tables underlying Table 1. However, a family of models was tested using both lower and higher thresholds. Higher prevalences represent the possibility of undetected false negatives. Very similar parameter estimates resulted from this exercise. Only under the extreme assumption of doubling the prevalences in Table 2, denoting that the contingency tables contain only half of the cases and that there was an equal number of false negatives who were undetected, is there a noticeable effect on the parameters. For example, h² for Alzheimer’s disease would become .62; c² , .35; e² , .02. However, this model fit quite poorly, χ² = 23.06 (df = 4, p < .0001). The fact that c² is increased under this latter assumption is consistent with prior demonstration that, if the disorder increases probability of enrollment, then c² will be underestimated and e² will be underestimated (31).

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<th>Table 1. Similarity of Monozygotic and Dizygotic Twin Pairs for Alzheimer’s Disease and for All Dementias</th>
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Notes: For Alzheimer’s disease, pairs were excluded if the partner had vascular dementia or a dementia due to another specified cause. Truncated pairs are those cases in which the partner had died prior to the proband’s age of onset.
Within-pair Differences in Age of Onset

Figure 2 shows all pairs used in the Alzheimer’s disease analyses with their ages of onset. As evident in the figure, age of onset can vary widely between members of a concordant pair. For concordant pairs, the within-pair difference in age of onset for Alzheimer’s disease ranged from 4 to 16 for MZs and from 1 to 12 for DZs. The means were 9.5 (SD = 5.87) for MZ and 5.6 (SD = 3.50) for DZ, a difference that was not statistically significant. In other words, only 56% of MZs and 50% of DZ cases were concordant within 5 years from the age when the first member of the pair became demented.

DISCUSSION

Concordance rates, intra-pair tetrachoric correlations, and model-fitting results with this registry-derived population-based sample of twins suggest that there is a marked heritable component to dementia of the Alzheimer’s type late in life. Concordance figures are based on ascertainment pairs, while correlations and model-fitting take the population into account. In particular, results from model-fitting allow quantification of the relative importance of genetic risk factors in late-onset Alzheimer’s disease. It bears emphasis that these variance estimates are “anonymous.” Thus, twin studies tell us how much influence genes have, taken altogether, but do not identify specific genes of importance.

One manner in which multiple hereditary factors may play a role in Alzheimer’s disease occurrence is suggested by a model of dementia that incorporates a neuropathological threshold (32). Attaining that threshold is a function both of cerebral reserve and onset of specific pathophysiological events. Genes may contribute either to the specific pathophysiological defect or to extent of cerebral reserve.

At the same time, we would not want to overemphasize a solely genetic model. Two findings point to the role of the environment. First, both the tetrachoric correlations and the structural modeling results point to twin similarity due to the environment (c2). These variance estimates are, again, “anonymous.” The Alzheimer’s disease literature details a number of risk and protective factors (33), but the analyses presented here do not incorporate specific exposures. Interpreting the fact that environmental factors emerged as shared influences rather than as nonshared influences (e2) does not mean that both members of the pair suffered from exposure to the same risk factor; rather, that both members of the pair shared a likelihood to be exposed to some factor that influenced their risk to develop dementia.

Second, the range of ages of onset within both MZ and DZ pairs is further evidence for environmental influences. Especially for identical pairs with discrepant ages of onset, the possible role of environmental factors is compelling. These results might even suggest a hypothesis that there are different etiologies for liability to the disease and for age of onset.

It is of interest to compare these findings from the Study of Dementia in Swedish Twins with other twin studies of Alzheimer’s disease. The Norwegian Twin Registry has been matched with records from geriatric services in old age homes, leading to the report of 83% concordance for 12 MZ pairs and 42% concordance for 24 DZ pairs (34). Probably due to case identification strategies, the Norwegian sample is somewhat older than ours. As has been pointed out (35), concordance rates can increase with the age of the sample. Further, this method of identifying cases would lead to high specificity but low sensitivity. In particular, cases may have been missed because they never came to the attention of service sites. The National Academy of Sciences Registry of Aging Twin Veterans (comprising males born 1917 to 1927) has been screened with methods analogous to ours, with probandwise concordance rates of 21% for 19 MZ pairs and 11% for 18 DZ pairs (36). However, the preva-

Table 2. Model Fitting Results for Liability to Dementia, Based on Contingency Tables With a Fixed Threshold

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</tr>
<tr>
<td>drop c2</td>
<td>.43</td>
<td>.43</td>
<td>.14</td>
<td>1.55</td>
<td>4</td>
<td>.82</td>
<td>-6.45</td>
</tr>
<tr>
<td>drop h2</td>
<td></td>
<td>.90</td>
<td>.10</td>
<td>4.33</td>
<td>5</td>
<td>.50</td>
<td>-5.67</td>
</tr>
</tbody>
</table>

Notes: h2 = additive genetic variance; c2 = shared environmental variance; e2 = unique environmental variance; AIC = Akaike’s Information Criterion.
TWIN STUDY OF ALZHEIMER’S DISEASE

There may well have been under-ascertainment due to influences in age of onset that we have observed, it might be interesting to consider separate genes for longevity and for the psychopathological changes associated with senile psychosis. Finally, there have been reports in the literature of single MZ pairs that have remained discordant for over 15 years (41,42).

There are major challenges in evaluating heritability for late-age-of-onset, low-prevalence disorders at a single period of time. Failure to detect all cases is one major concern. Available resources precluded our undertaking either in-person or telephone assessment with every individual in the population, and we cannot be certain of the sensitivity of the case ascertainment procedure. However, convergence between the prevalence of dementia in this sample and that reported by various population-based surveys provides some assurance that the method of identifying cases was successful.

Because Alzheimer’s disease has a late age of expression, many presumably predisposed partners will have died of other causes before the proband becomes affected, potentially biasing the estimate of heritability. For this reason, we considered the data in two ways, both including and excluding pairs where the partner died before the proband’s age of onset. When these pairs were excluded, the estimate for genetic variance decreased and the estimate for shared environmental variance increased. This result may well simply reflect twin similarity for survival, because pairs who are discordant for over 15 years (41,42).

Another concern is diagnosis, and the difficulty in accurately diagnosing Alzheimer’s disease. We may have been either too inclusive or too exclusive with respect to Alzheimer’s disease diagnoses. Consequently, we have presented results based on diagnosed Alzheimer’s disease but also for late-age-of-onset cases of Alzheimer’s disease had a diagnosis of dementia (43). This rate is not substantially different from the concordance rate found here for DZ twin pairs.

Prior to these studies, a volunteer National Institutes of Health sample of 22 twin pairs showed a concordance rate of 41% for MZ and 40% for DZ (39). Mean age at workup was 70. Although the sample was relatively large compared to case studies of single individuals, the likelihood of volunteer bias makes interpretation difficult. The earliest twin study was that of Kallman (40), who reported 42.8% concordance for MZ and 8.0% concordance for DZ co-twins with respect to senile psychosis. This diagnosis excluded presenile cases (at that time, the term ‘Alzheimer’s disease’ was reserved for presenile dementia) and combined what would now be regarded as Alzheimer’s disease, vascular dementias, and other more rare late-onset dementias. Thus, the Kallman results can most appropriately be compared to all dementias.

Interestingly, he held that the best model for understanding heritability of dementia might be to consider separate genes for longevity and for the psychopathological changes associated with senile psychosis. Finally, there have been reports in the literature of single MZ pairs that have remained discordant for over 15 years (41,42).

One of the main challenges in evaluating heritability for late-age-of-onset, low-prevalence disorders at a single period of time is failure to detect all cases. This is a major concern. Available resources precluded our undertaking either in-person or telephone assessment with every individual in the population, and we cannot be certain of the sensitivity of the case ascertainment procedure. However, convergence between the prevalence of dementia in this sample and that reported by various population-based surveys provides some assurance that the method of identifying cases was successful.

The chief methodological concern, above all, is whether undetected cases differ from detected cases in any fashion that would influence concordance. We did not find any bias in this regard. Further reassurance stems from comparison of the dizygotic concordance figure to the rate of cases among siblings of individuals with Alzheimer’s disease, who also on average share half of their genes. A re-analysis of 7 case-control studies has shown that 18.5% of siblings of late-onset cases of Alzheimer’s disease had a diagnosis of dementia (43). This rate is not substantially different from the concordance rate found here for DZ twin pairs.

Because Alzheimer’s disease has a late age of expression, many presumably predisposed partners will have died of other causes before the proband becomes affected, potentially biasing the estimate of heritability. For this reason, we considered the data in two ways, both including and excluding pairs where the partner died before the proband’s age of onset. When these pairs were excluded, the estimate for genetic variance decreased and the estimate for shared environmental variance increased. This result may well simply reflect twin similarity for survival, because pairs who are discordant for age at death are eliminated from the sample.

Another concern is diagnosis, and the difficulty in accurately diagnosing Alzheimer’s disease. We may have been either too inclusive or too exclusive with respect to Alzheimer’s disease diagnoses. Consequently, we have presented results based on diagnosed Alzheimer’s disease but also for late-onset dementia. At the same time, neuropathological confirmation indicates that the diagnoses are largely accurate.

Other concerns include refusals on the part of co-twin partners to participate and the fact that the study is cross-sectional. These methodological considerations all would mainly lead to an underestimate of heritability. For exam-
ple, if all pairs are followed longitudinally, some partners, although currently intact, may develop dementia.

Although ours is a large twin study of dementia, because Alzheimer’s disease is a low-prevalence disorder, sample size is small with respect to statistical power, and confidence intervals are large. Numbers of cases become particularly small when pairs are dropped from Alzheimer’s disease analyses due to the partner’s presenting with another demen
ting disorder or to the partner’s death before the proband’s age of onset. It should be cautioned too that shared environment, although currently intact, may develop dementia.

related, because twin pairs share the same age. However, a larger sample would be required in order to determine the contribution of age to the \( c^2 \) term. Further, genetic-environment correlation and gene-environment interaction are not evaluated. Finally, it should be noted that heritability estimates, because they are anonymous, may include both genetic influences specific to Alzheimer’s disease and genetic influences related to cerebral reserve. Nonetheless, across the various analyses, results consistently indicated significant heritability.

In conclusion, our findings indicate a substantial genetic susceptibility in late-onset Alzheimer’s disease cases, reflecting multiple defects or variations in brain metabolism that may ultimately lead to a similar pathological cascade. At the same time, it appears that environmental factors play a key role with respect to both occurrence and age of onset, either through their effects on cerebral reserve or through modifying the disease cascade, an observation with implications for strategies to delay onset or to prevent disorder entirely.

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Address correspondence to Dr. Margaret Gatz, Department of Psychology, University of Southern California, Los Angeles, CA 90089-1061. E-mail: gatz@rcf.usc.edu

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