ORIGINAL ARTICLE

A Family Study of Alzheimer Disease and Early- and Late-Onset Depression in Elderly Patients

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Background: The substantial symptomatic overlap between depression and dementia in old age may be explained by common genetic vulnerability factors.

Methods: We investigated this idea by comparing the occurrence of both disorders in first-degree relatives of 78 patients with Alzheimer disease (AD), of 74 with late-onset depression (onset age of ≥60 years), of 78 with early-onset depression, of 53 with comorbid lifetime diagnoses of AD/depression, and of 162 population control subjects. Diagnostic information on their 3002 relatives was obtained from structured direct assessments and from family history interviews.

Results: The 90-year lifetime incidence of primary progressive dementia was significantly higher in relatives of patients with AD (30%) and comorbid AD/depression (27%) than in relatives of patients with early-onset (21%) or late-onset (26%) depression, or of controls (22%) (P=.01). Lifetime incidence of depression was significantly higher in relatives of patients with early-onset depression (13%) than in relatives of patients with AD (10%) or controls (9.0%) (P=.006). Lifetime incidence of depression was similar in control relatives and in relatives of those patients with comorbid AD/depression (8.6%). Relatives of patients with late-onset depression also showed similar occurrence of depression until the age of 80 years, but the figure increased sharply thereafter to 19.1% by the age of 90 years.

Conclusions: Primary progressive dementia and early-onset depression represent clinical entities with distinct inheritance. Late-onset depression does not share substantial inheritance in common with dementia or with early-onset depression, but does show modest familial clustering.

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DEPRESSION IS common in old age,[1,2] and cognitive dysfunction, including severe memory deficit, is frequent in elderly patients with depression.[3-7] Likewise, depressive symptoms are often seen in those with Alzheimer disease (AD).[8-10] The cause of such symptom overlap in geriatric depression and AD is unclear, but it may reflect common genetic antecedents. Especially when genetic causes are suspected, family studies can inform the causative classification of psychiatric disorders in that relatives of subjects with one causative entity should show an increased risk of this, but not other, conditions. By contrast, when 2 or more syndromes have common genetic antecedents, their relatives should show increased risks of all such related syndromes, but not of other disorders.[11]

Such reasoning presupposes significant familial aggregation for the disorders in question, eg, AD and depression. This presupposition is justified for AD and for early-onset depression (EOD), but is less secure for late-onset depression (LOD). First-degree relatives of patients with AD show a 2- to 3-fold increased occurrence of primary progressive dementias (PPDs), as contrasted with control relatives.[12-20] Similarly, increased risks have been reported for depression in relatives of (mostly young) patients with bipolar I and II disorder and for relatives of patients with early-onset unipolar depression.[21-24] When the proband's onset of depression is later, the findings are less consistent. Maier and colleagues[25] showed a higher risk of depression in first-degree relatives of patients with LOD (onset age of ≥60 years) than in relatives of controls. Other groups[25-29] have reported lower loads of depression in relatives of probands with LOD than in relatives of patients with EOD, but there are exceptions.[30] Brodaty and coauthors[31] observed lower risks of depression in parents, but not in siblings, of patients with LOD.

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PATIENTS AND METHODS

RECRUITMENT OF PATIENTS, CONTROLS, AND THEIR FIRST-DEGREE RELATIVES

Between January 1, 1992, and October 31, 1995, and between January 1, 1996, and December 31, 1998, we recruited in sequence patients aged 60 years or older from the clinics of the University of Bonn, Bonn, and the University of Mainz, Mainz, Germany, respectively. The resulting patient sample included 78 with AD, 78 with EOD, 74 with LOD (onset age of ≥60 years), and 53 with AD/depression (comorbid patients). In the same years, we recruited 162 control subjects who were group matched to the patient sample on age, sex, and educational background. With the support of the cities' census agencies, we used a weighted, stratified, systematic sampling approach to select matched controls at random from the inhabitants' registers of the 2 communities (**Table**). We contacted the control subjects by mail or, if they did not respond, by telephone to administer a personal interview. The patients and controls were asked to provide names and addresses for all first-degree relatives. All procedures involving contact with human subjects were approved by the relevant local ethics committees, and informed consent was obtained for each stage of direct contact. We also asked the relatives whom we interviewed to obtain assent from their unavailable family members for their inclusion in the analyses.

Because PPD is rare before the age of 50 years (in 1775 relatives aged <50 years, only 1 showed PPD), we required that all patients and controls have at least one first-degree relative aged 50 years or older available for interview. Among eligible patients, the participation rate was then 87%.[40] Without prior information on the availability of control relatives, we could not calculate a comparable participation rate among eligible controls. Nonparticipant patients were broadly similar to participants on age, sex, and marital status, but had slightly higher educational attainment.[40] Educational background was similar, however, for each group of patients and for controls. As expected, patients with EOD were slightly younger than the other groups (Table).

Given the high prevalence of many mental disorders, several investigators[41-43] have noted that the use of disease-free controls can artificially inflate distinctions in case-control comparisons. Others[44] have, therefore, proposed that selected (disease-free) and unselected controls should be used, but this approach creates additional statistical comparisons. Because we were interested in comparing risks in various relative groups vs the general population, we followed the conservative practice of not requiring that controls be disease free. An unselected general population control panel also enabled the use of a single large group of control relatives for all comparisons. Accordingly, our 162 control individuals included 22 with dementia, 8 with EOD, and 9 with past or current LOD.

FIRST-DEGREE RELATIVES

Two first-degree relatives asked not to be included in the study, and their data were consequently excluded from analysis. The 445 study probands then had 3002 first-degree relatives (Table). We could not learn whether 210 (7.0%) of these relatives were living or dead but assumed that many were long deceased or lost to follow-up, probably as a result of wartime conditions. Of the remaining 2792 relatives, 1236 (44.3%) were deceased (Table). We succeeded in interviewing 775 (49.8%) of the remainder. Living relatives of probands with EOD were somewhat younger, while educational attainment was slightly lower among interviewed relatives of patients with LOD (Table). We interviewed a higher proportion of female than male relatives (52.7% vs 43.5%; $\chi^2_1 = 14.2$; $P < .001$), but there were no important differences in sex composition of the various relative groups. Ostensibly psychiatrically ill relatives of control subjects (but not of patients) were less available for interview than their healthy counterparts.[40] To prevent an awareness bias when comparing relatives of patients and controls, we, therefore, included source of information (interview vs family history information only) as a covariate in the survival analyses. We also made separate comparisons using interviewed and unavailable relatives and obtained identical results.

DIAGNOSTIC ASSESSMENT

The clinical examination of the patients consisted of personal and family histories, neurological and medical assessments, an extensive laboratory workup, electroencephalography, computed tomography or magnetic resonance imaging, and other tests if indicated. The patients, controls, and their available first-degree relatives were

Continued on next page

Few studies have examined the familial aggregation of AD and depression simultaneously. The available studies[32-36] have often shown increased occurrence of depression and other psychiatric disorders among the relatives of patients with AD, and vice versa. Two groups[37,38] reported an increase in depression among relatives of probands with AD, specifically when the latter had comorbid depression. Another study[39] confirmed this finding only for female probands with AD. Important limitations of these studies, and probable reasons for their inconsistent results, may be their limited size (in most instances) and their investigation of only 1 or 2 disorders in patients or their relatives. Most studies also used the family history method rather than more precise family study methods, in which ill relatives are directly examined.

To our knowledge, we undertook the first family study of PPD and depressive syndromes among relatives of probands with AD, EOD, and LOD, among relatives of patients with comorbid AD/depression, and among relatives of matched population controls. We investigated the following hypotheses:

1. Alzheimer disease and EOD have different genetic antecedents and, therefore, different patterns of familial aggregation. Accordingly, relatives of probands with AD will have higher loads of PPD than relatives of patients with EOD or controls. Relatives of probands with EOD will show more depression than relatives of patients with AD or controls.

2. Late-onset depression belongs to the broad spectrum of depressive disorders. Therefore, relatives of

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assessed using the Composite International Diagnostic Interview[45] to assign lifetime *DSM-III-R* diagnoses for major psychiatric disorders.[46] To detect and diagnose dementia, we interviewed patients, controls, and their relatives older than 50 years using the Structured Interview for the Diagnosis of Dementia of the Alzheimer Type, Multi-Infarct Dementia and Dementias of Other Aetiology.[47] Both instruments include the Mini-Mental State Examination.[48] To detect depression and dementia in living and deceased relatives, we also used the Family History Questionnaire[49] and the Family Dementia Risk Questionnaire.[14,50] We obtained family history information from spouses and all interviewed relatives. The interviewers were medical students in their final years of training or junior physicians. They had been trained in a 4-week clinical clerkship on a geropsychiatric ward, and had participated in a comprehensive training course, including at least 10 supervised training interviews. The interviewers were "blind" to the patients' (and control subjects') diagnoses. To maintain this blindness, they did not ask for information about the probands. Final diagnoses and age at onset were assigned using the best-estimate procedure[51] according to the consensus judgment of 2 experienced psychiatrists (R.H. and A.P.) who remained blind to the identity of all probands and relatives.

We rarely obtained identical diagnoses for a relative from combinations of 2 or more direct interviews or family history interviews. We, therefore, combined lifetime diagnoses into broad categories for which agreement was high. Diagnoses of major depression included *DSM-III-R* codes 296.20 to 296.36. We diagnosed PPD (codes 290.00-290.30) rather than AD in relatives because the latter can only be diagnosed after a clinical workup. Interrater reliability of the direct interview data was satisfactory for major depression (Cohen $\kappa=0.67$; 95% confidence interval, 0.37-1.00) and for PPD (Cohen $\kappa=1.00$; 95% confidence interval, 0.78-1.00). Interinformant reliability of family history–based diagnoses was moderate for PPD (Cohen $\kappa=0.58$; 95% confidence interval, 0.48-0.68) but weaker for depression (Cohen $\kappa=0.26$; 95% confidence interval, 0.14-0.38).[52] Compared with direct interview results, family history data showed limited sensitivity but good specificity, namely, sensitivity and specificity of 20.8% and 98.4% for dementia and 34.0% and 97.1% for depression, respectively. These sensitivity estimates reflect the comparison of family history information obtained from all available informants vs a direct interview of those who could participate in the latter. The sensitivity of family history interviews increased substantially with severity or duration of illness.[53] The low sensitivity of family history information will reduce observed lifetime incidence, but it should not affect comparisons of risks across relatives of various patient groups or controls unless the sensitivity varied according to the diagnosis in the proband. To control for the latter effect, we included the source of information (direct assessment vs family history data) as a covariate when comparing survival curves. Like Kendler and colleagues,[54] we found increased sensitivity in the reporting of depression by relatives who had themselves experienced a depressive illness.[53] To avoid spurious familial aggregation resulting from this problem, we discarded the family history information obtained from 93 relatives with one of the diagnoses under study. Other diagnostic information, including direct interview results, remained available for these relatives.

STATISTICAL ANALYSES

Group comparisons used the χ^2 statistic, analysis of variance, and the Scheffé tests. To compare the risks of depression and PPD in relatives of the various groups of patients and controls, we calculated Kaplan-Meier survival curves. Multivariate Cox proportional hazards regression analyses were then used according to the study hypotheses.[55] We cite resulting hazard ratios (HRs) instead of corresponding χ^2 values for individual comparisons if the HR can be interpreted, ie, if $P\leq.05$ and $df=1$. For clarity, the final analyses were restricted to include only variables with significant influence on familial loads for depression and PPD, namely, sex and source of information (family history vs direct interview). Because proportional hazards analysis relies on the (not necessarily justified) assumption of proportionality in the effects of various predictor variables across multiple groups, we also examined differences among the several Kaplan-Meier curves using distribution-free Mantel-Haenszel statistics[56] (the weakness of this method being its lack of consideration to covariates or to examination of interaction effects). Unless otherwise stated, all χ^2 statistics have 1 *df*. The conventional threshold for statistical significance (α) was taken as $P<.05$ (2 tailed). A priori power calculations had shown that we would then need about 60 families in each group to afford a probability of 80% ($\beta=.20$) of detecting significant differences among the survival curves.

probands with LOD will show more depression than relatives of controls, but they will not show higher risks of PPD than relatives of patients with EOD or controls.

3. Alternatively, LOD belongs to the broad spectrum of dementing disorders. Therefore, relatives of patients with LOD will show more PPD than relatives of probands with EOD or controls, but they will not show more depression than relatives of patients with AD or controls.

4. Patients with a history of AD/depression (comorbid cases) are genetically vulnerable to dementia and depression. Therefore, the relatives of such comorbid probands will show more PPD than the relatives of patients with EOD or controls, and more depression than the relatives of probands with AD or controls.

RESULTS

PPD IN RELATIVES

Figure 1 presents Kaplan-Meier curves of estimated PPD-free survival among relatives of the various patient and control groups. Proportional hazards regression analysis revealed significant differences in disease-free survival among relatives of the different proband groups (Wald $\chi^2_4=17.0$; $P=.002$). Risks were increased in relatives of patients with AD and of patients with comorbid AD/depression compared with control relatives (HR, 2.38 [$P<.001$] and 2.06 [$P=.01$], respectively). Sex had no significant influence on the risk of PPD ($\chi^2=1.86$; $P=.17$). Direct interviewing increased the chance of detecting PPD

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Description of 445 Patients and Control Subjects and 2792 First-Degree Relatives by Diagnoses of Patients and Controls*

Variable	Patients' Diagnoses: AD	AD/Depression	Early-Onset Depression†	Late-Onset Depression‡	Control Subjects	Group Comparison (ANOVA or Pearson χ^2 Test)
Subject group	A	B	C	D	E	. . .
No. of Subjects	78	53	78	74	162	. . .
Age, y	75 ± 9	73 ± 9	66 ± 7	72 ± 8	73 ± 11	F_4 = 11.0, P<.001; C<A, B, D, and E§
Female sex, %	74	66	71	70	61	χ^2_4 = 5.3, P = .26
Education, y‖	9.9 ± 2.0	9.3 ± 2.2	9.8 ± 2.0	9.2 ± 2.1	9.5 ± 2.0	F_4 = 0.6, P = .65
First-degree relatives						
Total No.	557	392	487	500	1066	. . .
No. with known age or age of death	520	347	465	440	1020	. . .
Age, y	60 ± 20	59 ± 19	56 ± 20	58 ± 20	58 ± 20	F_4 = 2.6, P = .03; C<A§
Female sex, %	51	48	50	45	51	χ^2_4 = 4.3, P = .36
Deceased	252	164	183	192	445	. . .
Age, y	65 ± 22	63 ± 20	67 ± 19	66 ± 21	66 ± 22	F_4 = 0.8, P = .52
Female sex, %	47	45	45	44	45	χ^2_4 = 0.4, P = .99
Living	268	183	282	248	575	
Age, y	56 ± 17	55 ± 17	49 ± 18	52 ± 17	53 ± 17	F_4 = 5.9, P = .001; C<A, B, and E§
Female sex, %	56	54	55	46	55	χ^2_4 = 7.4, P = .12
Interviewed	143	97	148	144	243	
Age, y	55 ± 15	54 ± 17	49 ± 17	52 ± 16	51 ± 16	F_4 = 3.4, P = .009; C<A§
Female sex, %	58	56	60	51	63	χ^2_4 = 5.6, P = .23
Education, y‖	10.2 ± 2.3	11.0 ± 2.5	10.1 ± 2.1	9.9 ± 2.4	10.6 ± 2.4	F_4 = 3.1, P = .02¶
Unavailable but living	125	86	134	104	332	. . .
Age, y	57 ± 18	56 ± 17	50 ± 19	52 ± 17	54 ± 18	F_4 = 1.0, P = .43
Female sex, y%	54	51	49	39	50	χ^2_4 = 5.8, P = .22

*Data are given as the mean ± SD unless otherwise indicated. ANOVA indicates analysis of variance; AD, Alzheimer disease; and ellipses, data not applicable.
†Age at onset is 60 years or younger.
‡Age at onset is older than 60 years.
§Post hoc comparisons: P<.05 (Scheffé test, Bonferroni corrected).
‖Time in school.
¶Post hoc comparisons: no significant group differences (P>.10; Scheffé test, Bonferroni corrected).

compared with family history information (HR, 2.3; P<.001), but this effect disappeared if an interaction term including source of data and sex was used. This term indicated that direct interview diagnoses of PPD were more sensitive than family history diagnoses in women (HR, 2.91; P<.001) but not in men. When the analyses were stratified by source of information, the diagnosis of the patient remained the only predictor for risk of PPD in relatives (for interviewed subjects vs those diagnosed by family history, χ^2_4=11.4 [P=.02] vs χ^2_4=10.6 [P=.03]).

Mantel-Haenszel statistics revealed similar results: the familial loads of PPD were different for the various groups of relatives (log-rank test χ^2_4=12.9; P=.01). Relatives of patients with AD showed increased risk of PPD compared with relatives of probands with EOD or LOD and controls (log-rank tests: AD vs EOD, χ^2=5.65, P=.02; AD vs LOD, χ^2=4.41, P=.04; and AD vs controls, χ^2=14.64, P<.001). Relatives of comorbid patients also showed increased risk of PPD compared with control relatives (log-rank χ^2=9.45; P=.002) and, suggestively, with relatives of probands with EOD and LOD (log-rank χ^2=3.52 [P=.06] and 2.37 [P=.12], respectively). Patients with AD and with comorbid AD/depression, therefore, appear relatively distinct from patients with EOD and with LOD and from controls for their familial loads of PPD. Relatives of patients with AD and of patients with AD/depression had indistinguishable familial loads of PPD (χ^2=0.10; P=.76), as did relatives of patients with LOD and EOD and control subjects (LOD vs controls, χ^2=1.24; EOD vs controls, χ^2=0.62; and LOD vs EOD, χ^2=0.06; $P \geq$.27 for all).

DEPRESSION IN RELATIVES

Figure 2 shows Kaplan-Meier curves for depression-free survival by relatives of patients and controls. Cox proportional hazards regression analysis again revealed that proband diagnosis significantly influenced relatives' risk of depression (Wald χ^2_4=14.5; P=.006). For relatives of patients with EOD vs control relatives, the HR was 1.64 (P=.04), whereas for relatives of patients with AD, the HR was 0.57 (P=.05). Relatives of probands with LOD and with comorbid AD/depression showed risks of depression similar to control relatives (χ^2=0.88 and 0.01, respectively; $P \geq$ .34). Female relatives showed more depression than male relatives (HR, 1.93; P<.001). Directly interviewed relatives also showed an apparently increased risk vs those assessed only by family history information (HR, 2.2; P<.001), but this effect did not vary substantially across proband groups. A significant interaction between sex and source of data (χ^2=7.33; P=.007) suggested that the difference in depression between female and male relatives was greater in relatives assessed by family history than in those who were interviewed (HR, 2.13 [P=.008] and 1.32 [P=.07], respectively). Interaction terms between proband diag-

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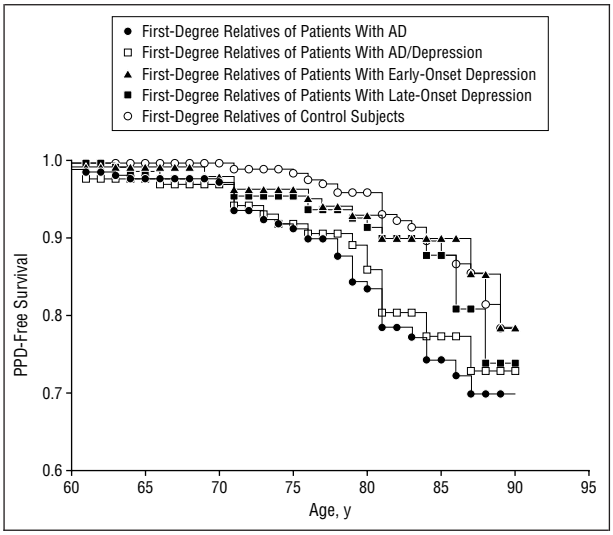

Figure 1. *Primary progressive dementia (PPD)–free survival up to the age of 90 years in first-degree relatives with known age or age of death by lifetime diagnosis of patients and control subjects, ie, in 520 relatives of 78 subjects with Alzheimer disease (AD), in 347 relatives of 53 subjects with comorbid AD/depression, in 465 relatives of 78 subjects with early-onset depression, in 440 relatives of 74 subjects with late-onset depression, and in 1020 relatives of 162 controls.*

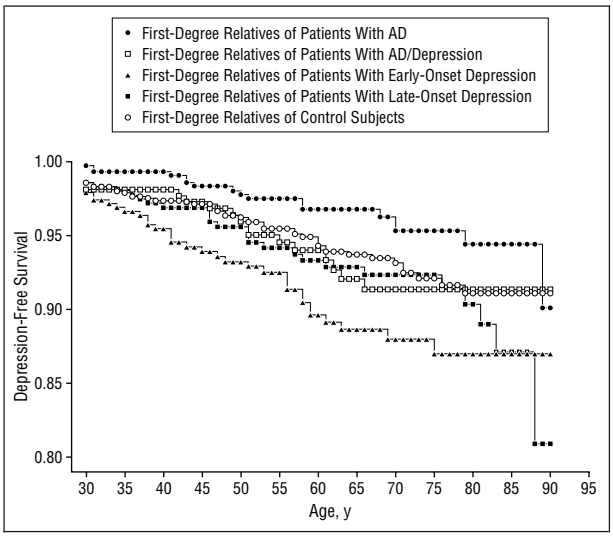

Figure 2. *Depression-free survival up to the age of 90 years in first-degree relatives with known age or age of death by lifetime diagnosis of patients and control subjects, ie, in 520 relatives of 78 subjects with Alzheimer disease (AD), in 347 relatives of 53 subjects with comorbid AD/depression, in 465 relatives of 78 subjects with early-onset depression, in 440 relatives of 74 subjects with late-onset depression, and in 1020 relatives of 162 controls.*

nosis and sex, or between diagnosis and source of data, were not statistically significant (χ^2_4=8.6 [P=.07] and 6.8 [P=.14], respectively).

Mantel-Haenszel statistics supported these results. The familial load of depression differed significantly by proband diagnoses (log-rank χ^2_4=14.5; P=.006). Relatives of patients with EOD showed the most depression compared with relatives of patients with AD and controls (log-rank χ^2=14.1 and 6.30, respectively; $P \leq .01$). However, comparisons of relatives of probands with EOD vs LOD or comorbid AD/depression were inconclusive (log-rank χ^2=1.41 [P=.23] and 2.45 [P=.12], respectively). Relatives of probands with AD showed the lowest occurrence of depression (log-rank tests: AD vs controls, χ^2=3.36, P=.07; AD vs EOD, χ^2=14.1, P<.001; AD vs LOD, χ^2=6.72, P=.01; and AD vs comorbid AD/depression, χ^2=3.42, P=.06). Patients with LOD, comorbid AD/depression, and controls did not differ in their familial loads of depression (LOD vs controls, χ^2=1.12, P=.29; comorbid patients vs controls, χ^2=0.06, P=.81; and LOD vs comorbid AD/depression, χ^2=0.35, P=.55). However, relatives of patients with LOD showed a small, but significant, increase in LOD after the age of 80 years. Of 64 relatives of patients with LOD, 4 (6%) developed depression after this age, as contrasted with 2 (2%) of 85 relatives of persons with AD, 1 (2%) of 65 such relatives of persons with EOD, and 0 of the 145 control relatives and the 51 relatives of probands with comorbid AD/depression (χ^2_4=11.5; P=.02).

COMMENT

In keeping with our first hypothesis, we found an increased risk of PPD in the relatives of patients with AD and of patients with comorbid AD/depression, compared with relatives of controls, but no such increase in relatives of probands with EOD. The observed familial aggregation of PPD is in full agreement with several earlier studies.[12-14,16-20] Like several other family studies on EOD,[21-24] we also found increased risk of depression in relatives of probands with EOD vs relatives of controls, but there was no such effect in relatives of patients with AD. These results suggest that AD and EOD are psychiatric disorders that share few, if any, common genetic antecedents.

In contrast with Maier and colleagues,[25] and in contrast with predictions of our second and third hypotheses, we found that probands with LOD did not show significant familial loading of either depression or PPD when compared with controls. Their relatives' occurrence of depression tended to be lower than in relatives of patients with EOD, and their load of PPD was substantially lower than in relatives of patients with AD. These results do not support the notion that LOD shares familial factors with either AD or EOD. There is, nevertheless, a slight but significant increase in the loading of LOD in the relatives of probands with LOD that is evident after the age of 80 years. These findings suggest that unique familial factors may predispose to the development of LOD.

Our fourth hypothesis was confirmed only in part, in that patients with comorbid AD/depression showed familial loading of PPD similar to that in patients with uncomplicated AD, but they showed no substantial increase in familial risk of depression.

The reduced risk of depression in relatives of patients with AD compared with relatives of controls was unexpected. This difference persisted when we restricted the control group to those free of disease. We conjecture that some protective factor(s) might reduce the risk of depression in these relatives of probands with AD or, alternatively, that our patients with AD and without comorbid depression might represent individuals selected for the absence of familial risk factors for depres-

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sion. We favor the latter interpretation because it is consistent with several family studies[37-39] showing an increased risk of depression in relatives of subjects with comorbid AD/depression compared with relatives of patients with uncomplicated AD. The similar observed risks of depression in relatives of patients with comorbid AD/depression and of controls might reflect the limited effect of familial factors on relatives' risk of depression, rendering difficult their detection in a comparison with population controls.

Selection bias and awareness bias are potential problems in this work, as in all family studies. We succeeded in administering a direct interview to only 775 of 3002 relatives, representing 49.8% of those living and 25.8% of the entire sample. Our observed proportion of missing data (210 relatives, or 7.0%) would be unlikely to bear substantially on results of survival analyses. To examine possible differences in the reported occurrence of illness in direct interview vs family history data, we compared results in a subsample of the first 531 relatives studied. Except for the relatives of controls,[40] we saw little effect of proband's diagnostic group on relatives' availability for direct interview. Consequently, and because the relatives' groups had comparable demographic characteristics, we doubt that differential participation had any undue influence on comparisons of disorders in the different relative groups.

The variables that affected the validity of diagnoses that relied on family history were disorder in the informant, age, and sex. Accordingly, we deleted information provided by diseased informants to prevent spurious familial aggregation. Differences in the age distribution of relatives were intrinsically considered through the use of survival analysis, while sex and the source of information were controlled by including them as covariates. All analyses, including those stratified by source of information (direct interview vs family history) and the use of a design that compared several groups of relatives (not only specific proband vs control relatives), led to consistent results. We are, therefore, confident that our findings are valid.

Our a priori power calculations relied on earlier studies that had compared familial loads of dementia in patients with AD and controls, and of depression in probands with EOD and controls. Accordingly, small differences between disorders with intermediate familial loads would not be expected to reach statistical significance. We, therefore, cannot exclude the possibility of small increases of the familial loadings of PPD or depression in relatives of subjects with LOD.

The observed familial aggregation of psychiatric disorders may be explained by shared environmental factors and by genetic risk factors that influence the illness susceptibility.[57] Broadly speaking, different disorders are likely to vary in the degree to which genetic and shared environmental factors contribute to their familial aggregation. Even so, genetic vulnerability factors are probably more important than shared environment when onset is characteristically in late life, as in AD and LOD. It is also likely that these prevalent late-onset conditions have heterogeneous causes and tend mostly to result from complex interactions of common genetic and environmental risk factors. These arguments should not detract substantially from the reported results and conclusions, which were based on comparisons across multiple groups of relatives. We acknowledge that our study could have been improved with inclusion of *APOE* (apolipoprotein E) genotypes for our probands and their relatives. Such genotypes were not included herein because we did not collect blood samples at the beginning of the study, and because some interviewed family members were reluctant to provide blood samples. Despite these limitations, we suggest that this is the largest and most comprehensive study yet published on familial aggregation and coaggregation of the common psychiatric disorders of old age. Our results suggest broadly that a family history of AD, EOD, and LOD all indicate an increased familial risk for the same, but not other, psychogeriatric disorders.

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