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FULL-LENGTH ORIGINAL RESEARCH

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Mood disorders in familial epilepsy: A test of shared etiology

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Summary

Objective: Mood disorders are the most common comorbid conditions in epilepsy, but the cause remains unclear. One possible explanation is a shared genetic susceptibility to epilepsy and mood disorders. We tested this hypothesis by evaluating lifetime prevalence of mood disorders in relatives with and without epilepsy in families containing multiple individuals with epilepsy, and comparing the findings with rates from a general population sample.

Methods: The Composite International Diagnostic Interview was administered to 192 individuals from 60 families, including 110 participants with epilepsy of unknown cause (50 focal epilepsy [FE], 42 generalized epilepsy [GE], 6 FE and GE, 12 unclassifiable) and 82 relatives without epilepsy (RWOE). Odds ratios (ORs) for lifetime prevalence of mood disorders in participants with versus without epilepsy were computed through logistic regression, using generalized estimation equations to account for familial clustering. Standardized prevalence ratios (SPRs) were used to compare prevalence in family members with general population rates.

Results: Compared with RWOE, ORs for mood disorders were significantly increased in participants with FE (OR = 2.4, 95% confidence interval [CI] = 1.1-5.2) but not in those with GE (OR = 1.0, 95% CI = 0.4-2.2). In addition, prevalence of mood disorders was increased in individuals with epilepsy who had ≥1 relative with FE. Compared with general population rates, mood disorders were significantly increased in individuals with FE but not in those with GE. Rates were also increased in RWOE, but not significantly so (SPR = 1.4, P = .14).

Significance: These findings are consistent with the hypothesis of shared genetic susceptibility to epilepsy and mood disorders, but suggest (1) the effect may be restricted to FE, and (2) the shared genetic effect on risk of mood disorders and epilepsy may be restricted to individuals with epilepsy, that is, to those in whom the genetic risk for epilepsy is "penetrant."

KEYWORDS
epilepsy, familial, mood, shared etiology

1 | INTRODUCTION

Mood disorders, including depression, are the most common comorbid conditions in epilepsy,[1,2] and impose substantial burdens including reduced quality of life, increased disability and healthcare utilization,[3] and heightened risk for suicidal ideation and attempts.[4] Moreover, individuals with comorbid mood disorders tend to have a worse seizure outcome than those without comorbid mood disorders.[5]

Although the comorbidity of epilepsy and mood disorders has been extensively studied, the cause of the comorbidity needs further clarification. One possible explanation

is the chronic psychosocial impact of epilepsy, including social stigma,[6] learned helplessness, and lack of control.[7] Moreover, epilepsy can lead to an acute state of depressed mood due to side effects of antiepileptic drugs[8] or seizure manifestations.[9] Finally, the comorbidity may be due to an underlying shared neurobiological pathogenesis, possibly involving the limbic system[10,11] or neurotransmitter function.[12] Demonstration of the "bidirectionality" of the association (ie, an increased risk of mood disorders in persons with epilepsy both before and after onset of epilepsy) supports the concept of shared pathogenic mechanisms.[13]

We took advantage of an ongoing study of familial epilepsy[14] to investigate the hypothesis that the comorbidity between epilepsy and mood disorders is due, in part, to a shared genetic susceptibility. Few studies have investigated this hypothesis. In our previous study of families with autosomal dominant epilepsy with auditory features (ADEAF) with mutations in the leucine-rich, glioma inactivated 1 gene (*LGI1*),[15] rates of current depressive symptoms were increased among mutation carriers with epilepsy, but not among mutation carriers without epilepsy. In another study, a family history of epilepsy was associated with affective disorders among individuals with childhood onset epilepsy.[16] However, neither study used a full diagnostic instrument nor assessed lifetime history of mood disorders, which is most important for assessing shared genetic risk.

In the current study, we used the Composite International Diagnostic Interview (CIDI)[17] to assess the lifetime prevalence of mood disorders in a set of families enriched for genetic influences on epilepsy because they contained multiple affected individuals. To evaluate evidence for a shared genetic susceptibility to epilepsy and mood disorders, we assessed the lifetime prevalence of mood disorders in relatives without epilepsy in these families, and compared it with lifetime prevalence in a general population sample. We also compared the lifetime prevalence of mood disorders in individuals with versus without epilepsy in these families (overall and by broadly defined epilepsy types), and assessed the relationship of lifetime prevalence of mood disorders to the type of epilepsy in the family.

Key Points

- In multiplex epilepsy families, lifetime prevalence of mood disorders was significantly increased in people with FE
- Lifetime prevalence of mood disorders was not increased in people with GE
- Lifetime prevalence of mood disorders was higher in people with epilepsy with versus without relatives with FE but not in those with versus without relatives with GE
- Lifetime prevalence of mood disorders was modestly (but not significantly) increased in relatives without epilepsy
- Results support the hypothesis of shared genetic risk for epilepsy and mood disorders that is specific for FE

2 | MATERIALS AND METHODS

2.1 | Participants

The participants were members of families containing either 2 living siblings or 3 or more living individuals with epilepsy of unknown cause, ascertained from ongoing genetic studies in the Epilepsy Family Study of Columbia University.[14] Potentially eligible families were identified from patients seen at the Columbia University Medical Center, referrals from neurologists at other institutions, and self-referrals in response to a study website or advertisement, primarily through the Epilepsy Foundation.[14] Families with known *LGI1* mutations or with clinical features consistent with ADEAF[18] were excluded. Clinical information for all family members was collected using a set of validated semistructured interviews, usually administered by telephone. Medical records were obtained from the patients' treating physicians and reviewed for seizure descriptions, histories of etiologic factors, and electroencephalographic (EEG) and neuroimaging data. Some patients were also given a brief neurologic examination and a study EEG. The final diagnosis of each subject was based on consensus review of all available information by 2 experienced epileptologists. To prevent bias, the epileptologists were blinded to information about other family members when they reviewed each subject's information.

For the present study, 84 eligible families were identified, each containing 2 or more living individuals with epilepsy of unknown cause. Potential participants included people with epilepsy of unknown cause (either focal epilepsy [FE], idiopathic generalized epilepsy [GE], both generalized and focal epilepsy, or unclassifiable epilepsy) and their first-degree relatives without epilepsy (RWOE). Families were excluded if no individual with epilepsy of unknown cause participated. A total of 548 individuals in 84 families containing an average of 2.8 individuals per family with epilepsy of unknown cause met initial inclusion criteria (234 individuals with epilepsy of unknown cause and 314 RWOE). To assess the degree to which lifetime history of mood disorders was increased in individuals with epilepsy within families containing multiple affected individuals, we used the RWOE as an internal comparison group. To determine whether the lifetime prevalence of

mood disorders was increased compared with the general population, we also included an external comparison group (see below).

Individuals meeting initial inclusion criteria were contacted by telephone and invited to participate. We attempted to reach each individual at least 5 times, at different times during the day and on weekends. For many subjects, a long time period (up to 20 years) had elapsed since last contact for the genetic study; hence, whenever necessary, we searched telephone and Internet databases for new addresses and telephone numbers. Consenting individuals were scheduled for a subsequent telephone interview. An experienced interviewer, blind to the individual's position in the pedigree and epilepsy history, administered the computerized lifetime version of the CIDI[17] via telephone. The CIDI is a comprehensive, fully standardized diagnostic interview aimed at detecting a lifetime history of various Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV) psychiatric diagnoses, created jointly by the World Health Organization and the former U.S. Alcohol, Drug Abuse, and Mental Health Administration, which has been used in large epidemiological studies. Our primary and secondary outcomes were lifetime prevalence of any mood disorder (defined as any major depressive disorder [MDD], dysthymia, or bipolar disorder) and MDD specifically. For diagnosis of these outcomes, we used both the depression and mania modules of the CIDI. The mood disorders section includes questions assessing for MDD (single and recurrent), bipolar disorder, and dysthymia. The mania module was used to rule out history of bipolar disorders (manic, mixed, or hypomanic episodes).

The study was approved by the Columbia University Medical Center Institutional Review Board; all subjects gave informed consent.

2.2 | General population sample

For the external comparison sample, we used data from the National Comorbidity Survey Replication (NCS-R).[19] The NCS-R is a nationally representative face-to-face household survey of 9090 respondents aged 18 years and older. The target population of the NCS-R was the civilian noninstitutionalized population residing in the 48 contiguous states. Consenting subjects were administered the DSM-IV version of the CIDI as in the current study.

2.3 | Statistical analyses

Data analyses were carried out using SAS software, version 9.3 for Windows (SAS Institute, Cary, NC, USA). We used logistic regression to compute odds ratios (ORs) for lifetime prevalence of any mood disorder in people with epilepsy (any epilepsy of unknown cause, GE, FE) using RWOE as the reference group. By design, the study participants were not independent, as multiple individuals were sampled within each family. To account for this familial clustering in our analyses, we used generalized estimating equations with exchangeable correlation structure, implemented in the SAS GENMOD procedure. We also repeated the analyses restricting the outcome to lifetime prevalence of MDD, excluding participants diagnosed with a mood disorder other than major depression (n = 4).

Variables considered for inclusion in the analyses as potential confounders were gender, marital status, education, age at CIDI interview, and total number of family members with epilepsy. Among RWOE, we assessed whether the prevalence of mood disorders differed according to their relationship to their first-degree relative(s) with epilepsy (parent, offspring, sibling, or multiple first-degree relatives with epilepsy). All associations were expressed as ORs with 95% confidence intervals (CIs).

We also generated unadjusted Kaplan-Meier failure curves to illustrate the cumulative incidence of mood disorders among participants; for these analyses, comparisons of incidence rates among subjects with FE or GE versus RWOE were made using the log-rank test. We performed Cox proportional hazards regression to evaluate differences between participants with epilepsy and RWOE in the risk of developing a mood disorder, using robust sandwich covariance matrix estimates to account for clustering. Follow-up time was defined by the time from birth until the self-reported age at incidence of mood disorders (for those who had a mood disorder) or age at interview (for those who did not have a mood disorder).

For comparisons with the general population sample, we computed standardized prevalence morbidity ratios (SPRs) applying the SAS PROC STDRATE procedure, using the NCS-R as the standard population. For this analysis, observed number of cases of mood disorders in each of the various subgroups of interest in our study (numerator) was divided by the number expected (denominator) based on gender- and age-specific (ages 18-29, 30-44, 45-59, ≥60 years) prevalence of mood disorders from the NCS-R.[20]

We also examined whether the likelihood of a lifetime history of mood disorders varied according to the type of epilepsy in the family. For these analyses, we computed ORs for mood disorders in participants with versus without ≥1 relative with FE, and with versus without ≥1 relative with GE.

3 | RESULTS

Of the 548 individuals who met initial criteria for inclusion, 145 (26.5%) were excluded before attempting contact

because they had died (22.1%), were unable to participate due to illness (1.4%), or had no participating relative with epilepsy of unknown cause (76.6%). We attempted to contact the remaining 403 individuals (222 epilepsy of unknown cause and 181 RWOEs). Of these, 271 (67.2%) were successfully contacted, and 192 (70.8% of those contacted) participated (110 epilepsy of unknown cause and 82 RWOEs). Individuals from 60 distinct families were interviewed; the number of interviewed relatives per family ranged from 1 to 18, with a mean of 3.2 (with epilepsy 1.8, range = 1-5; RWOE 1.4, range = 0-13). Among individuals with epilepsy of unknown cause, 42 (38%) had GE, 50 (45%) had FE, 6 (5%) had both, and 12 (11%) were unclassifiable. For analyses of specific epilepsy types, individuals with both GE and FE or unclassifiable epilepsy were excluded.

Seventy (36%) participants met criteria for lifetime history of mood disorders, which included MDD only (n = 62), MDD plus dysthymic disorder (n = 4), dysthymic disorder only (n = 1), and bipolar disorder (n = 3). Women were more likely to meet criteria for mood disorders than men ($P = .04$). Lifetime prevalence of mood disorders declined with advancing age, but the linear trend was not significant ($P = .06$). Prevalence of mood disorders was not associated with either marital status or educational attainment.

We examined sociodemographic variables by epilepsy history (Table 1). Compared with RWOE, individuals with epilepsy were more likely to be women (65% vs 54%, $P = .09$), were younger (although not significantly so; mean age = 48.5 vs 52.9 years, $P = .37$), and were less likely to be married (48% vs 66%, $P = .06$). Education was comparable in participants with and without epilepsy. Based on these findings, and because women are twice as likely as men to be diagnosed with major depression across a variety of settings,[21] we considered gender, but not age, education, or marital status, to be a potentially confounding variable and included it in our regression analyses.

Cumulative incidence of mood disorders was significantly higher in participants with epilepsy than in RWOE among all participants ($P = .01$ by log-rank test) and among women ($P = .006$), but not among men ($P = .47$; Figure 1). Cumulative risk of mood disorders was higher for participants with FE than for either those with GE or RWOE, both in the total sample and in women only, after adjustment for multiple comparisons. However, no significant differences were observed in the men.

Controlling for gender, ORs for lifetime prevalence of mood disorders were significantly increased in participants with FE versus RWOE (OR = 2.4, 95% CI = 1.1-5.2) and in FE versus GE (OR = 2.7, 95% CI = 1.1-6.5; Table 2A). In contrast, the odds of mood disorders did not differ significantly between participants with GE and RWOE (OR = 0.9, 95% CI = 0.4-2.2). The ORs for MDD followed a similar pattern as for any mood disorder, but were slightly lower (Table 2B). Hazard ratios computed by Cox proportional hazards regression were similar to the ORs computed by logistic regression (data not shown). Among the 45 individuals with epilepsy who met criteria for lifetime history of mood disorders, 40 reported age of onset of mood disorders, of whom 4 had onset of mood disorders before onset of epilepsy (3 with FE and 1 with unclassified epilepsy).

We used the external comparison group to assess whether the lifetime prevalence of mood disorders in the familial epilepsy cohort (both individuals with epilepsy and RWOE) was increased, compared with the general population, as reflected by prevalence in the NCS-R (Table 3).[19] The SPRs were adjusted for gender and age separately, because the NCS-R did not report rates stratified simultaneously by age and gender. Lifetime prevalence of mood disorders in the familial epilepsy sample was higher than the corresponding NCS-R rates, as indicated by SPRs > 1. The total SPR for RWOE was 1.4 ($P = .14$), and the gender- and age-adjusted SPRs were similar. The SPRs for GE were approximately 1.4; none was significant. In contrast, the age- and gender-adjusted SPRs for FE were significant (total SPR = 24, $P = .002$).

We also examined whether the type of epilepsy in affected family members (≥1 relative with FE or ≥1 relative with GE) was associated with the likelihood of mood disorders (Table 4). Among RWOE, prevalence of mood disorders was not associated with having ≥1 relative with either GE or FE specifically. Among participants with epilepsy, however, prevalence of mood disorders was significantly associated with having ≥1 relative with FE (OR = 2.4; Table 4). Although not significant, this pattern also appeared to be present among participants with either GE (OR = 1.9) or FE (OR = 1.3). The number of relatives with FE and the number of relatives with GE within each family were negatively correlated ($r = -.74$, $P < .0001$), reflecting the tendency for families to be "concordant" for epilepsy type.[22] Consistent with this relationship, prevalence of mood disorders was inversely associated with having ≥1 relative with GE among all relatives with epilepsy (OR = 0.4) and among those with GE specifically (OR = 0.2; Table 4).

We also examined whether the lifetime prevalence of mood disorders among RWOE was related to the total number of individuals with epilepsy within the family. Such an association, if observed, could reflect either an effect of increasing genetic heritability or psychosocial factors related to family burden. Among RWOE, prevalence of mood disorders was not associated with either total number of family members with epilepsy of any type, or number of family members with GE or FE specifically

TABLE 1 Characteristics of familial epilepsy cohort

Characteristics	Relatives without epilepsy, n = 82	All epilepsy of unknown cause, n = 110[a]	Generalized epilepsy, n = 42	Focal epilepsy, n = 50
Gender, n (%)				
Male	38 (46.3)	38 (34.5)	14 (33.3)	17 (34.0)
Female	44 (53.7)	72 (64.5)	28 (66.7)	33 (66.0)
Age at interview				
Mean y ± SD	52.9 ± 15.8	48.5 ± 16.7	46.0 ± 16.0	48.5 ± 16.1
Age, n (%)				
18-29 y	9 (11.0)	17 ((15.5)	7 (16.7)	7 (14.0)
30-44 y	14 (17.1)	23 (20.9)	13 (31.0)	9 (18.0)
45-59 y	35 (42.7)	48 (43.6)	15 (35.7)	27 (54.0)
≥60 y	24 (29.3)	22 (20.0)	7 (16.7)	7 (14.0)
Education				
Mean y ± SD	15.2 ± 3.1	14.8 ± 2.7	14.1 ± 2.6	15.2 ± 2.6
Years, n (%)				
8-12	17 (20.7)	26 (23.6)	13 (31.0)	9 (18.0)
13-16	40 (48.8)	58 (52.7)	22 (52.4)	27 (54.0)
≥17	25 (30.5)	26 (23.6)	7 (16.7)	14 (28.0)
Marital status, n (%)				
Married	56 (65.1)	53 (48.2)	23 (54.8)	20 (40.0)
Not married	30 (34.9)	57 (51.8)	19 (45.2)	30 (60.0)
Mood disorders, n (%)				
Yes	25 (30.5)	45 (40.9)	13 (31.0)	27 (54.0)
No	57 (69.5)	65 (59.1)	29 (69.0)	23 (46.0)
Major depression, n (%)				
Yes	24 (29.3)	42 (38.2)	12 (28.6)	25 (50.0)
No	58 (70.7)	68 (61.8)	30 (71.4)	25 (50.0)

SD, standard deviation.

[a]Includes 6 subjects identified as having both focal and generalized epilepsy and 12 subjects with unknown type.

(data not shown). We also found no significant differences in prevalence of mood disorders among RWOE according to their relationship to a family member with epilepsy (unaffected parent, child, or sibling of an individual with epilepsy, or unaffected individual with multiple relatives with epilepsy).

4 | DISCUSSION

In this study of families containing multiple individuals with epilepsy, the lifetime prevalence of mood disorders was significantly increased in individuals with FE, compared with either individuals with GE or RWOE. Similarly, compared with rates from the NCS-R, which represent rates in the general U.S. population, the rate of any mood disorder was increased in individuals with FE, but not in individuals with GE. Moreover, lifetime prevalence of mood disorders was increased among participants with epilepsy who had ≥1 relative with FE, but not among those who had had ≥1 relative with GE. Lastly, among RWOE, we found suggestive evidence for increased prevalence of any mood disorder, compared with rates in the general population based on the NCS-R (SPR = 1.4; Table 3).

How do these results clarify the various explanations for the comorbidity of epilepsy and mood disorders? The specificity of our findings to individuals with FE but not GE argues against a psychosocial effect of having a disabling, stigmatized disorder. This explanation would imply a greater psychosocial burden in FE than in GE, possibly resulting from greater illness severity in FE. However, in our sample, illness severity does not appear to be greater in FE than GE. Approximately half of those in the current study also participated in another recent study and were

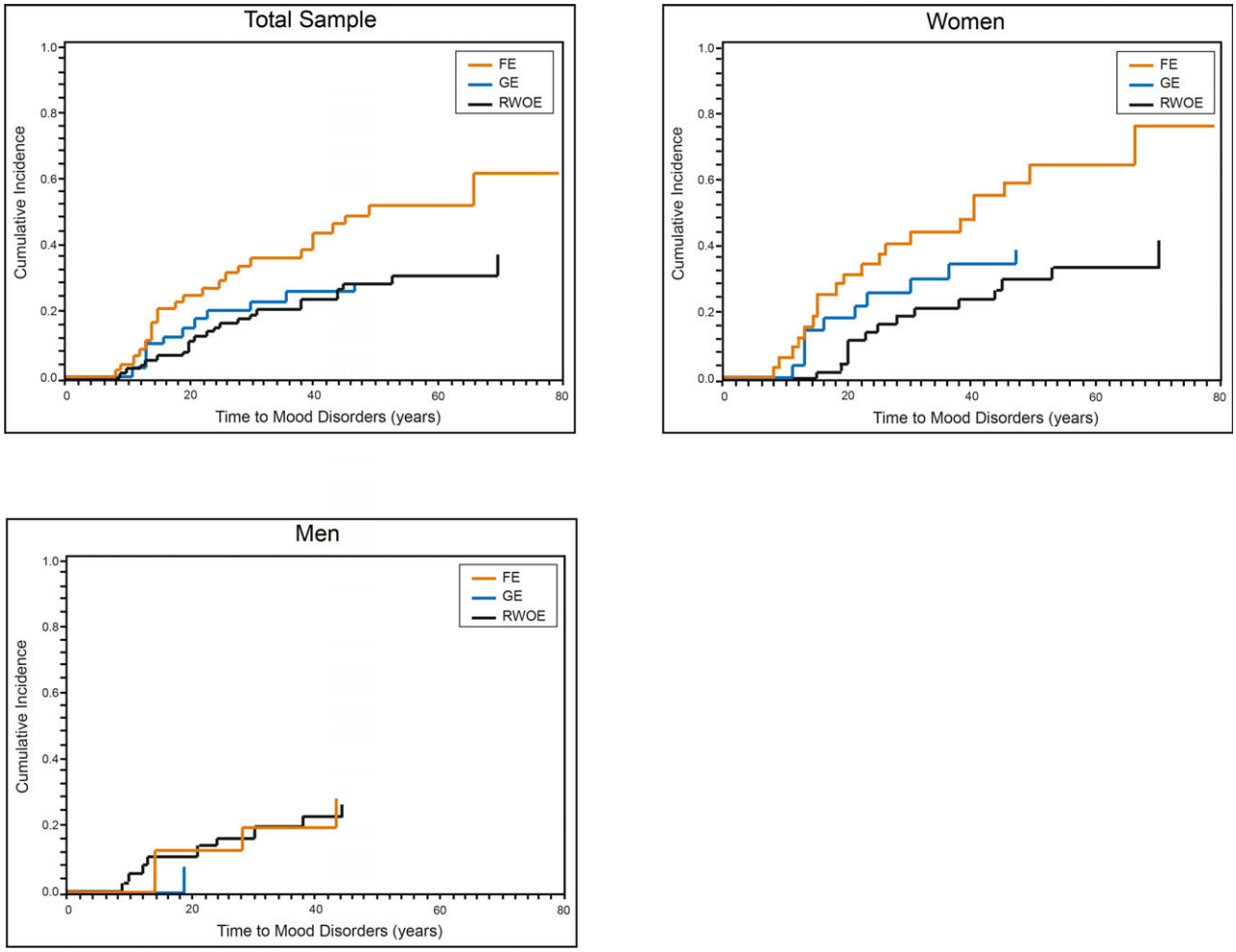

FIGURE 1 Kaplan-Meier failure curve of cumulative risk of mood disorders by epilepsy history, stratified by gender. FE, focal epilepsy; GE, generalized epilepsy; RWOE, relatives without epilepsy

asked about their lifetime number of seizures and time since last seizure.[23-26] In this subsample, individuals with FE and GE did not differ in either of these epilepsy severity measures (Table S1).

Our finding of marginally increased prevalence of mood disorders in RWOE compared to the general population is consistent with either a shared genetic susceptibility to mood disorders and epilepsy or a psychological burden of having multiple relatives with epilepsy. A recent literature review provides evidence that several negative consequences of epilepsy are likely to extend to family caregivers of patients with epilepsy.[27] Having a relative with epilepsy is associated with considerable emotional distress and imposes economic liability on other members of the family, especially on family caregivers.[28] However, our findings appear to be inconsistent with psychological burden as an explanation for the increased prevalence of mood disorders among RWOE. If psychological burden was the explanation, we would have expected prevalence of mood disorders in RWOE to be related to number of relatives with epilepsy and biological relationship to a person with epilepsy (sibling, parent, or child), which we did not observe. However, a limitation of these analyses is that we do not have information on the caregiving status of the family members without epilepsy or the family environment that might ameliorate or exacerbate the burden of illness.[29]

Our study was limited by its cross-sectional design, in which diagnoses of mood disorders were obtained from retrospective recall. Although individuals with epilepsy may be more likely than those without epilepsy to recall a past mood disorder, we have no reason to believe that recall would be differential by epilepsy type. Another constraint was the limited data on clinical seizure features. As cited above, we had severity and frequency data on approximately 50% of the individuals, but we did not have information on treatments for epilepsy (eg, medications, surgery, vagal nerve stimulation) and their side effects. These findings may not be generalizable to other individuals with epilepsy, because the participants came from

TABLE 2 ORs for mood disorders in familial epilepsy cohort by epilepsy history

	Unadjusted			Adjusted for gender		
	OR	**95% CI**	***P***	**OR**	**95% CI**	***P***
A. Any mood disorder						
Any epilepsy (n = 110) vs RWOE (n = 82)	1.5	0.8-2.7	.21	1.4	0.7-2.6	.31
GE (n = 42) vs RWOE (n = 82)	1.0	0.45-2.3	.96	0.9	0.4-2.2	.90
FE (n = 50) vs RWOE (n = 82)	2.5	1.2-5.4	.02	2.4	1.1-5.2	.03
FE (n = 50) vs GE (n = 42)	2.2	1.0-4.8	.06	2.7	1.1-6.5	.03
B. Major depressive disorder						
Any epilepsy (n = 107) vs RWOE (n = 81)	1.4	0.7-2.6	.32	1.3	0.7-2.5	.44
GE (n = 41) vs RWOE (n = 81)	0.9	0.4-2.2	.90	0.9	0.4-2.0	.75
FE (n = 48) vs RWOE (81)	2.4	1.1-5.3	.03	2.3	1.0-5.3	.04
FE (n = 48) vs GE (n = 41)	1.9	0.8-4.5	.12	2.4	0.9-6.1	.07

CI, confidence interval; FE, focal epilepsy; GE, generalized epilepsy; OR, odds ratio; RWOE, relatives without epilepsy.

TABLE 3 Comparison of lifetime prevalence of mood disorders in familial epilepsy cohort with the National Comorbidity Survey

	Unadjusted			Gender-adjusted			Age-adjusted		
	SPR	**95% CI**	***P***	**SPR**	**95% CI**	***P***	**SPR**	**95% CI**	***P***
RWOE	1.4	0.9-2.0	.14	1.4	0.9-2.0	.14	1.5	0.9-2.1	.10
Any epilepsy of unknown cause	1.9	1.4-2.5	.001	1.8	1.3-2.4	.002	1.9	1.3-2.4	.002
GE	1.4	0.7-2.4	.27	1.4	0.6-2.1	.32	1.4	0.6-2.2	.30
FE	2.5	1.6-3.5	.002	2.4	1.5-3.3	.002	2.4	1.5-3.3	.002

CI, confidence interval; GE, generalized epilepsy; RWOE, relatives without epilepsy; SPR, standardized prevalence ratio.

families with familial epilepsy. However, study of these families is particularly advantageous for investigating our hypotheses. We ascertained lifetime prevalence of mood disorders using the CIDI, a comprehensive, structured diagnostic interview. Finally, we had a relatively large sample size that enabled us to compare prevalence of mood disorders among individuals with focal and generalized epilepsy.

Although the present study does not include families with *LGI1* mutations or with suspected ADEAF, our findings are compatible with the results from our previous study of ADEAF due to mutations in *LGI1*.[15] In the previous study, current depressive symptoms (as opposed to lifetime prevalence reported here) were increased in mutation carriers with FE but not in mutation carriers without epilepsy, compared with family members who did not have a risk-raising mutation. Similarly, in the present study of familial epilepsy families, lifetime prevalence of mood disorders was increased, compared with general population rates, in individuals with FE but not in RWOE. Moreover, in a recent study that included approximately 50% of subjects from this dataset, prevalence of current depressive symptoms was lower in married-in individuals (3.9%) than in biologic relatives without epilepsy, although the difference was not significant (age-adjusted prevalence ratio = 0.7, 95% CI = 0.19-2.56, $P = .50$).[26]

In summary, our results are generally consistent with the hypothesis of shared genetic susceptibility to mood disorders and FE (but not GE). Among participants with FE, the prevalence of mood disorders was significantly increased compared with either individuals with GE or RWOE, and the rate of any mood disorder was increased compared with rates in a general population sample. Among individuals with epilepsy, prevalence of mood disorders was significantly associated with having 1 or more relatives with FE. These results are unlikely to be explained fully by side effects of antiepileptic medications,[8] epilepsy-related felt stigma,[30] or impaired quality of life and psychosocial functioning,[31,32] because individuals with generalized epilepsy probably experience similar complications and difficulties related to living with epilepsy. They provide support for the concept that comorbidity results from shared pathogenic mechanisms between mood disorders and focal epilepsy, possibly mediated by changes in neurotransmitters or structural abnormalities of the limbic circuit.[10,11]

On the other hand, our findings in RWOE appear to be inconsistent with the hypothesis of shared genetic

TABLE 4 ORs for mood disorders according to type of epilepsy in family

	0 relatives with focal epilepsy		≥1 relative with focal epilepsy			
Person at risk of mood disorder	**n**	**n with mood disorder**	**n**	**n with mood disorder**	**OR (95% CI)**	***P***
Relative without epilepsy	22	7	60	18	0.7 (0.18-2.91)	.64
Any type of epilepsy	41	12	69	33	2.4 (1.01-5.48)	.05
Generalized epilepsy	26	7	16	6	1.9 (0.50-7.53)	.34
Focal epilepsy	11	5	39	22	1.3 (0.31-5.58)	.71
	0 relatives with generalized epilepsy		**≥1 relative with generalized epilepsy**			
Person at risk of mood disorder	**n**	**n with mood disorder**	**n**	**n with mood disorder**	**OR (95% CI)**	***P***
Relative without epilepsy	28	12	54	13	0.4 (.14-1.31)	.14
Any type of epilepsy	48	26	62	19	0.4 (0.16-0.92)	.03
Generalized epilepsy	9	6	33	7	0.2 (0.03-0.89)	.03
Focal epilepsy	33	18	17	9	1.0 (0.30-3.30)	.99

CI, confidence interval; OR, odds ratio controlling for gender.

susceptibility to FE and mood disorders. RWOE who have ≥1 relative with FE are expected to have an increased frequency of genetic variants that raise the risk for FE, and if these variants also increase the risk for mood disorders, it would be expected that RWOE would have an increased risk of mood disorders. However, because these relatives do not have epilepsy, they must be "nonpenetrant" for the FE-related genetic variants. Hence, under a hypothesis of shared genetic susceptibility, a possible explanation for the lack of increased risk of mood disorders in these RWOE is that the same (genetic or environmental) factors that protected them from developing epilepsy also protected them from developing mood disorders.

Many tools are now available to screen for mood disorders in patients with epilepsy.[33] Mood disorders in people with epilepsy are associated with poorer seizure control, and several antidepressants, particularly selective serotonin reuptake inhibitors, have anticonvulsant properties.[34] Despite the substantial morbidity associated with mood disorders and the availability of appropriate screening tools and therapeutic treatments, mood disorders remain underdiagnosed and undertreated in patients with epilepsy.[35] Clinicians treating patients with epilepsy should evaluate their patients, particularly those with focal epilepsy, for mood disorders and initiate appropriate treatment.

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DISCLOSURE

None of the authors has any conflict of interest to disclose We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

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