

Original Articles

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Migraine and Major Depression: A Longitudinal Study

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SYNOPSIS

Recent epidemiologic studies have reported an association between migraine and major depression. Little is known about the mechanisms that link the two disorders, or the natural history of their co-occurrence. We examined the association between migraine and major depression in a sample of young adults, using longitudinal data.

Method: A random sample of 1,007 young adults (21-30 years of age) members of a large HMO in Southeast Michigan was interviewed in 1989; 97% of the sample were reinter-viewed 3.5 years later, in 1992. A structured diagnostic interview was used to elicit information on DSM-III-R major depression and IHS migraine in lifetime (in the 1989 interview) and during the 3.5 year follow-up interval (in the 1992 interview). Using Cox-proportional hazards models with time-dependent covariates, we estimated the relative risk for major depression associated with prior migraine and the relative risk for migraine associated with prior major depression.

Results: In this sample of young adults, the incidence of migraine per 1,000 person years, based on the prospectively gathered data, was 5.0 in males and 22.0 in females. The estimated relative risk for major depression associated with prior migraine, adjusted for sex and education, was 3.2 (95% CI 2.3-4.6). The adjusted relative risk for migraine associated with prior major depression was 3.1 (95% CI 2.0-5.0).

Conclusions: The study provides the first body of evidence that the previously observed cross-sectional association between migraine and major depression can result from bidirectional influences, with each disorder increasing the risk for first onset of the other. The explanation that major depression in persons with migraine represents a psychologic response to migraine attacks would have been more plausible had we found an influence only from migraine to depression. By diminishing the plausibility of a simple causal explanation for the migraine-depression comorbidity, the findings favor the shared mechanisms explanation.

Key words: migraine, major depression, epidemiology

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INTRODUCTION

Recent epidemiologic studies have reported associations between migraine and psychiatric disorders, primarily major depression and anxiety disorders.¹⁻⁶ Although research to date has focused primarily on the migraine - major depression comorbidity, little is known about the mechanisms that link the two disorders, or the natural history of their co-occurrence. Two alternative explanations might account for the association: (1) migraine might cause major depression or, conversely, might be caused by it. Thus, for example, depression in persons with migraine might be a psychologic reaction to recurrent disabling headache attacks; (2) migraine and major depression might share etiologic factors, genetic or environmental. Abnormalities related to the neurotransmitter serotonin have been suggested as a neurochemical basis for migraine as well as for major depression.⁷⁻⁹

In this study, we examined the association between migraine and major depression in a sample of young adults, assessed in 1989 and again in 1992. Using survival analysis with time-dependent covariates, we examined whether the previously reported lifetime association between the two disorders results from a unidirectional influence of one disorder on the other or from a bidirectional influence, with each disorder increasing the risk for first onset of the other. Although observational studies cannot establish causality, they can produce evidence that would dampen the plausibility of some proposed mechanisms and enhance the plausibility of others. Evidence that prior history of migraine increases the risk for major depression, but that major depression does not increase the risk for migraine would support a controlling role of migraine on major depression and weaken the plausibility that the two disorders share an underlying etiology. Conversely, evidence of bidirectionality, specifically, that migraine increases the risk for major depression and that major depression increases the risk for migraine, would strengthen the hypothesis of shared-etologies at the expense of the hypothesis of a causal link.

Baseline data on lifetime history and follow-up data covering the 3.5 year interval were combined to produce estimates of the conditional risk for first onset major depression as a function of prior history of migraine and the conditional risk for first onset of migraine as a function of prior major depression. The availability of follow-up data, which covered a relatively brief period and were therefore less likely to be influenced by memory errors, provided an opportunity to evaluate the accuracy of estimates based on the lifetime data.

METHODS

A random sample of 1,200 was drawn from all 21-30 year-old members of a large HMO in southeast Michigan. A total of 1,007 (84%) were interviewed in person in 1989. Follow-up interviews were conducted approximately 3.5 years later, with 979 of the respondents, 97.2% of the sample, excluding two who left the country permanently, one who died, and one who was deleted due to a psychotic illness. The median age of the sample at baseline was 26 years, 62% were female, 80% were white. A small minority, 3.7% had not completed high school, 21% had completed high school, 46% had some college education and 29.3% were college graduates.

The NIMH-Diagnostic Interview Schedule (DIS), revised to cover DSM-III-R disorders,¹⁰ was used at baseline to measure lifetime history of common psychiatric disorders. Follow-up interviews covered psychiatric symptoms that had occurred during the 3.5 year interval since baseline. Detailed description of the NIMH-DIS and information on its reliability and validity have been previously reported.¹¹⁻¹³ The NIMH-DIS is a structured interview designed to be administered by trained lay interviewers. An extensive training program was used to assure close adherence to the questionnaire and the sequence of follow-up probes. Interviewers in the follow-up study were blind to the information gathered at baseline and to the hypotheses tested in the study. Interviews were conducted in respondents homes; those who moved out of the area between baseline and follow-up were interviewed by telephone.

Major depression is defined in DSM-III-R as a condition characterized by the presence of at least five from a list of nine depressive symptoms occurring within the same 2-week period, with at least one of the symptoms pertaining to a depressed mood or loss of interest or pleasure. The following symptom groups are listed in the DSM-III-R definition of major depression: dysphoria, loss of interest or pleasure, weight loss or weight gain, insomnia or hypersomnia, psychomotor agitation or retardation, fatigue, feelings of worthlessness or excessive guilt, concentration problems, suicidal ideations or attempts,

The baseline and follow-up interviews included a sequence of questions on defining features of migraine, adapted from the diagnostic criteria published by the International Headache Society, Headache Classification Committee.¹⁴ These criteria are:

- A. At least 5 attacks.
- B. Headache attacks lasting more than 4 hours.
- C. At least two of the following features: (1) unilateral pain; (2) pulsation; (3) inhibition or prohibition of daily activities; (4) aggravation by routine physical activity.
- D. At least one of the following: (1) nausea or vomiting; (2) photophobia and phonophobia.

For both major depression and migraine, age at first episode was ascertained in persons who met criteria for the disorders.

Statistical Analysis. The analysis of the association between migraine and major depression was preceded by displays of the cumulative incidence of the two disorders. The cumulative incidence of migraine and of major depression were estimated by Kaplan-Meier (K-M) survival analysis, a nonparametric estimator for censored data.^{15,16} The censored subjects were persons who have not developed the disorder of interest by the end of the observation period. The K-M method estimates the cumulative survival distribution, i.e., the probability of not having the disorder, at every time point for which there was at least one uncensored observation. Because our interest was in the incidence of the disorder (rather than of not having the disorder), we calculated the complement of the survival estimate (i.e., one minus the estimated probability of not having the disorder). The observed lifetime cumulative incidence of migraine and of major depression were estimated on the basis of the combined baseline and follow-up data. K-M survival analysis, with time defined as respondents' age, was used to estimate the cumulative incidence of either disorder from the earliest to the last case, up to approximately 33 years of age. The 3.5 year incidence during the follow-up interval was estimated on persons who started the follow-up period with no prior history of the disorder under study. In these analyses, time was defined as number of years since baseline. K-M curves were compared, using the logrank test.¹⁷

Cox-proportional-hazards models for censored survival data, with age of migraine onset as a time-dependent covariate, were used to estimate the relative risk for major depression associated with prior migraine.¹⁸⁻²⁰ The parameter estimates (betas) in the proportional hazards model are regression coefficients, from which relative hazards, or estimated relative risk, can be obtained. In this study, the relative risk for major depression associated with migraine compares the risk in persons with prior history of migraine to the risk in persons with no prior history of migraine at a specified point in time. An advantage of the Cox-proportional-hazards model with time-dependent covariates is that it permits us to take into account the age of onset of migraine in relation to the onset of major depression. In this analysis, time was defined as respondents' age, thereby providing age adjustment of the relative risk estimates.²¹ Additional analysis included also sex and education as fixed covariates. Two- and 3-way interactions were tested in separate models and found to be non-significant. To estimate the relative risk for migraine associated with prior major depression, the same approach was applied, using migraine as the dependent variable and major depression as the time-dependent covariate.

The relative risk for major depression associated with prior migraine and the relative risk for migraine associated with prior major depression were estimated on the combined longitudinal data gathered at baseline and at follow-up. Compared to the prospective data, the combined longitudinal data provide more precise estimates, given the larger person-time pool, and a broader age range (i.e., up to age 33) to which inferences can be made. The prospective data, gathered at follow-up, while probably more accurate and free of recall error, covered only incidence cases occurring in persons 22 to 33 years of age and cannot inform on persons with earlier onset of the disorders under study. To address the concern that the retrospective data gathered at baseline might have distorted the estimates based on the combined data, results based on the retrospective data alone were compared to those based on the prospective data.

RESULTS

Observed Lifetime Cumulative Incidence of Migraine and Major Depression. Estimates of the observed lifetime cumulative incidence of the disorders under study are based on the combined longitudinal data which cover all onsets experienced by the respondents, from the earliest to the last case up to 33 years of age. Of the total sample of 1,007 young adults, 174 had a history migraine

at any time in their lives, 34 males and 140 females. The number who met criteria for major depression was 190, 49 males and 141 females. The lifetime cumulative incidence of migraine and of major depression, estimated with K-M survival analyses appear in Table 1. At age 33, the cumulative incidence of migraine was 19.5% and of major depression, 22.5%. With respect to each disorder, the curve in females exceeded significantly that in males ($P < .001$, logrank test).

Figure 1 presents the K-M survival curves of migraine in males and females up to age 33. The cumulative percents were similar between the sexes up to age 14, when they were 4.4% in males and 3.9% in females. They began to diverge after 14 and by age 20 the proportions with history of migraine was 12.4% in females vs. 6.2% in males. The gap was even greater at age 30, with 23.8% of females vs. 9.4% of males having met criteria for migraine.

Figure 2 depicts the survival curves of major depression in males and females up to age 33. From early adolescence to the early twenties, the cumulative percent of major depression was slightly higher in females than males. At age 22, the cumulative incidence of major depression was 7.5% in males and 10.5% in females. After age 22, the increase of major depression in females with increasing age exceeded that in males, so that at

Table 1
Cumulative Incidence of Migraine and Major Depression up to Age 33 Years
(Percent and 95% Confidence Interval)

		Migraine	Major Depression
TOTAL	(N=1007)	19.47 (16.70-22.25)	22.49 (19.43 - 25.56)
Males	(N=388)	9.39 (6.33 - 12.46)	13.98 (10.23 - 17.74)
Females	(N=619)	25.90 (21.85- 29.95)	27.87 (23.53 - 32.22)

Estimated in Kaplan-Meier survival analyses with time defined as subjects' age.

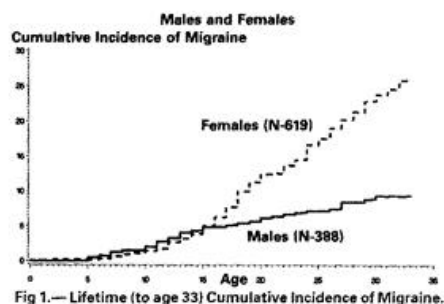


Fig 1.— Lifetime (to age 33) Cumulative Incidence of Migraine.

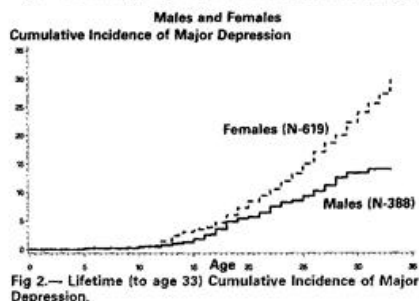


Fig 2.— Lifetime (to age 33) Cumulative Incidence of Major Depression.

age 30, the cumulative incidence of major depression in females was 24.2% and in males 13.3%.

The 3.5-Year Incidence of Migraine and Major Depression. Estimates of the 3.5 year incidence of migraine and major depression are based on the prospectively gathered follow-up data and describe onsets only during the third decade of life. Table 2 presents the cumulative incidence of migraine and of major depression for the total sample, by sex and by age. Of the 979 young adults with follow-up data, 128 had a history of migraine at baseline. Of the 851 at risk, there were 45 new cases of migraine during the 3.5 years follow-up period, 39 females and 6 males. The 3.5 year incidence of migraine, estimated by the K-M survival method, was 5.29% (95% CI 3.78-6.79), 1.74% (95% CI 0.36-3.13) in males and 7.69% (95% CI 5.37-10.01) in females. The incidence per 1,000 person-years was 4.98 (95% CI 1.8-10.9) in males and 22.00 (95% CI 15.6-30.0) in females. The percent females developing migraine overtime was significantly higher than males ($P = .0002$, logrank test). The 3.5 year cumulative incidence of migraine in younger persons (i.e., 22-26 years of age) was 6.68% (95% CI

Table 2
Three-and One-Half Years Incidence of Migraine and Major Depression in Young Adults

	Migraine	Major Depression
TOTAL	(N) (851)	(846)
	% (95% CI) 5.29 (3.78 - 6.79)	6.50 (4.84 - 8.16)
Sex: Males	(N) (344)	(335)
	% (95% CI) 1.74 (0.36 - 3.13)	3.58 (1.59 - 5.57)
Females	(N) (507)	(511)
	% (95% CI) 7.69 (5.37 - 10.01)	8.41 (6.01 - 10.82)
Age: 22-26	(N) (404)	(396)
	% (95% CI) 6.68 (4.25 - 9.12)	6.31 (3.92 - 8.71)
27-33	(N) (447)	(450)
	% (95% CI) 4.03 (2.20 - 5.85)	6.67 (4.36 - 8.97)

Estimated in Kaplan-Meier survival analyses with time defined as number of years since baseline.

4.25-9.12) and in older persons (27-33 years of age), 4.03% (95% CI 2.20-5.85). The difference in the curves of older and younger persons approached statistical significance ($P = .084$, logrank test).

Of the follow-up sample of 979, 133 persons with a history of major depression at baseline were deleted, leaving 846 at risk for major depression during the follow-up period. Of this subset, 55 new cases of major depression were ascertained, 43 females and 12 males. The 3.5 year incidence of major depression, estimated with the K-M survival analysis, was 6.50% (95% CI 4.84-8.16), 3.58% (95% CI 1.59-5.57) in males and 8.41% (95% CI 6.01-10.82) in females. The difference between the two curves was statistically significant ($P = .0056$, logrank test). Little difference in the incidence of major depression was observed between younger (i.e. 22-26 years of age) and older subjects (27-33 years of age), 6.31% (95% CI 3.92-8.71) vs. 6.67% (95% CI 4.36-8.97), respectively. The incidence per 1,000 person-years was 10.2 (95% CI 5.27-17.85) in males and 24.0 (95% CI 17.4-31.92) in females, figures similar to those reported by Eaton et al. for young adults in the ECA panel participating in the one year follow-up.²²

The Estimated Risk of Major Depression Associated with Prior Migraine. The risk for major depression associated with migraine was estimated on the combined longitudinal data gathered at baseline and at follow-up. Figure 3 displays two K-M survival curves of major depression, one in persons with migraine (N=174) and the other in persons who never had migraine (N=833). The cumulative incidence of major depression at age 33 in persons with migraine was 53.0% (95% CI 43.6-62.4) and in persons with no migraine, 15.9% (95% CI 13.0-18.7). Based on these curves, the relative risk for major depression in persons with migraine vs. no migraine was 3.8 (95% CI 2.9-5.1) ($P = .0001$). This estimate can be considered as the "crude" relative risk, as it is unadjusted for the age

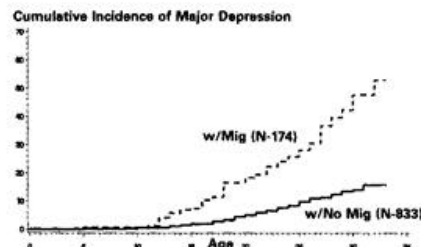


Fig 3.— Lifetime (to age 33) Cumulative Incidence of Major Depression in Persons With and Without History of Migraine.

of onset of migraine in relation to the onset of major depression.

In Table 3 appear the adjusted relative risk estimates, calculated in Cox-proportional hazards models, with migraine as a time-dependent covariate and sex and education as fixed covariates. Because this analysis stipulates that migraine onset must precede major depression, 12 cases in which the onset of both disorders occurred in the same

Table 3
Relative Risk (RR) for Major Depression Associated with Migraine from Cox-Proportional-Hazards Models with Time-Dependent Covariates (N=995)

		RR	(95% CI)	P value
Model I	Migraine	3.6	(2.6 - 5.2)	.0001
Model II	Migraine	3.4	(2.4 - 4.8)	.0001
	Sex (Female)	1.8	(1.3 - 2.5)	.0010
Model III	Migraine	3.2	(2.3 - 4.6)	.0001
	Sex (Female)	1.7	(1.2 - 2.5)	.0014
	Education (< college)	1.2	(0.9 - 1.7)	.183

year were deleted, leaving a subset of 995. Taking into account the age of onset of migraine (Model I) resulted in a slight decrease in the "crude" relative risk, from 3.8 to 3.6. Adjusting additionally for sex and education (Model III) the relative risk was 3.2. Other results of interest are that females had a significantly higher risk for major depression than males, but the effect of education on major depression was not significant.

Sex-specific Cox-proportional-hazards analyses revealed that the relative risk for major depression associated with prior migraine was increased significantly in both sexes, 3.4 (95% CI 1.5-7.8) and 3.0 (95% CI 2.0-4.6) in males and females, respectively.

The Estimated Risk of Migraine Following Major Depression. Figure 4 displays the K-M survival curves of migraine in persons with major depression (N= 190) and in persons with no major depression (N=817). The cumulative incidence at age 33 of migraine in persons with major depression was 46.4% (95% CI 37.5-54.7) and in persons with no major depression, 13.4% (95% CI 10.8-16.0). The "unadjusted" relative risk for migraine, based on these survival curves, was 4.1(95% CI 3.1-5.6) ($P = .0001$). Estimates from three Cox-proportional-hazards models, with major depression as the time-dependent covariate, are presented in Table 4. Relative risk for migraine, adjusted for age of major depression in relation to migraine onset (Model I), was 3.5. The relative risk for migraine, controlling also for the effects of sex and education (Model III), was reduced slightly to 3.1. The results also

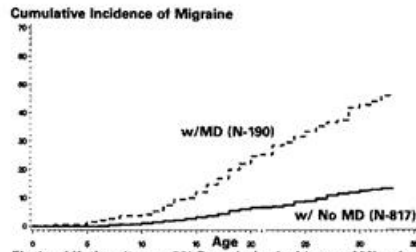


Fig 4.— Lifetime (to age 33) Cumulative Incidence of Migraine in Persons With and Without History of Major Depression.

Table 4

Relative Risk (RR) for Migraine Associated with Major Depression from Cox-Proportional-Hazards Models with Time-Dependent Covariates (N=995)

		RR	(95% CI)	P value
Model I	Major Depression	3.5	(2.2 - 5.6)	.0001
Model II	Major Depression	3.3	(2.1 - 5.3)	.0001
	Sex (Female)	2.8	(1.9 - 4.2)	.0001
Model III	Major Depression	3.1	(2.0-5.0)	.0001
	Sex (Female)	2.7	(1.8 -4.1)	.0001
	Education (< college)	1.8	(1.3 - 2.6)	.0014

show that the risk for migraine in females was nearly 3-fold greater than in males, and that persons with less than college education were nearly 2-fold more likely to develop migraine than those who completed college.

Sex-specific analyses revealed that the relative risk for migraine associated with prior major depression in males was 4.5 (95% CI 1.3-16.0) and in females, 2.9 (95% CI 1.8-4.8).

Comparisons of the Prospective and Retrospective Data. In Table 5 appear the relative risk estimates for major depression associated with migraine and for migraine associated with major depression, based on the retrospective (baseline) data alone and the prospective (follow-up) data alone. Using the retrospective data as the basis for estimating the strength of the association between the two disorders, we tested results from the prospective analysis in terms of their agreement with the previous estimates. The relative risks based on the prospective data were not significantly different from those based on the retrospective data, according to one sample z-tests. Thus, there is no evidence in these data that the estimates from the combined longitudinal data were biased by inaccuracies in the retrospective data. The two components in the combined data yielded similar results regarding the association between migraine and major depression

Table 5

Relative Risk (RR) Estimates* from the Prospective Data Alone and the Retrospective Data Alone

	Prospective	Retrospective	P-value**
	RR For Major	Depression Following	Migraine
Migraine	4.8 (2.7 - 8.4)	3.3 (2.1 - 5.2)	.202
Adjusted for sex & education	4.1 (2.2 - 7.4)	2.9 (1.9 - 4.7)	.280
RR For Migraine Following Major Depression			
Major Depression	3.8 (1.9-7.6)	4.1 (2.3-7.4)	.803
Adjusted for sex & education	3.3 (1.6-6.6)	3.8 (2.1-6.7)	.692

*From Cox-proportional hazards models with time-dependent covariates; 95% confidence intervals in parentheses.

**P-values from one sample z-test, comparing prospective estimates to retrospective estimates.

DISCUSSION

Analysis of the longitudinal data on migraine and major depression in this sample of young adults revealed that (1) migraine and major depression had similar cumulative incidence curves; (2) with respect to both disorders, the estimates in females exceeded significantly the corresponding estimates in males; (3) by age 30, the cumulative incidence of migraine and of major depression were approximately 20% in females and 10% in males; (4) the estimated risk for first onset of major depression in persons with prior history of migraine was 3.2-fold higher than in persons with no prior history of migraine; (5) Conversely, the estimated risk for first onset of migraine in persons with prior history of major depression was 3.1-fold higher than in persons with no prior history of major depression; (6) the association of each disorder with prior history of the other applied equally to males and females, although each of the two disorders was more common in females than in males.

In this analysis, we relied on the entire longitudinal data, combining lifetime data gathered retrospectively at baseline and prospective data gathered 3.5 years later. Comparisons of estimates based on the retrospective data to those based on the prospective data supported the conclusion that the two components in the longitudinal data set yielded similar results. The advantage of the combined data is in the greater precision of the estimates they yield, due to the larger total person-years covered, and the potential for generalizability to persons with onset of the disorders at any age up to the end of the third decade of life.

Estimates of the incidence of migraine in persons 22 to 33 years of age, based on the prospectively gathered data—22.0 in females and 5.0 in males per 1,000 person-years—support the previous observation that females display a later age of onset and a continued emergence of new cases through the third decade of life, and that males display an earlier age of onset and few new cases during the third decade.^{23,24} Despite the sex difference in the risk for migraine with increasing age, the association with major depression did not differ between the sexes.

Previous interpretations of the associations between migraine and psychopathology have generally preferred the shared mechanisms explanation, citing findings from studies on biologic markers, observations regarding the efficacy of tricyclic and monoamine oxidase inhibiting anti-depressants in both disorders, and evidence suggesting that dysfunction in serotonergic and adrenergic neurotransmitter systems might be involved in both.^{9,25-27} The hypothesis that the association between migraine and major depression reflects a psychological response to disabling migraine attacks has not received support in previous research.^{9,28}

This study provides the first body of evidence that the previously observed cross-sectional association between migraine and major depression might result from bidirectional influences, with each disorder increasing the risk for first onset of the other. A previous report, based on retrospective data, on the chronology of migraine and major depression in persons with the two disorders has suggested that the onset of major depression generally follows the onset of migraine.⁴ In this study as well, the majority of the comorbid cases, 54.5%, reported that migraine preceded major depression, whereas 30% reported that major depression preceded the onset of migraine and 15.5% reported the onset of both disorders in the same year. Nonetheless, the estimated relative risk for first onset of migraine conditional on prior history of major depression was as high as the estimated relative risk for first onset of major depression in persons with prior history of migraine.

What do the findings of bidirectional influences between migraine and major depression mean? Clearly, the explanation that major depression in persons with migraine is a psychological response to disabling migraine attacks, would have been more plausible had we found an influence only in one direction, i.e., from migraine to subsequent major depression. A causal explanation for the observed bidirectional influences would require that each disorder cause the other disorder by a separate mechanism. While not inconceivable, a complex explanation of this sort is not readily available. Thus, by diminishing the plausibility of a simple causal explanation for the migraine-major depression comorbidity, the findings favor the shared mechanisms explanation. An alternative hypothesis to the shared mechanisms might be that the comorbid migraine cases represent a distinct category, different from migraine alone. Research on neurobiology in patients with migraine and major depression vs. patients with migraine alone might shed light on this question.

The observation that migraine is associated also with anxiety disorders and that a high percent of persons with migraine and major depression meet criteria for an anxiety disorder^{2,4} has not been addressed in this analysis. The co-occurrence of major depression and anxiety in persons with migraine is not unique, as associations between major depression and specific anxiety disorders, including panic disorder, obsessive-compulsive disorder, generalized anxiety disorder, and phobia have been documented in clinical and community samples.²⁹⁻³² Difficulties in separating anxious from depressive symptoms and anxiety disorders from major depression, concurrently and overtime, have been noted previously,^{32,33} Evidence that the association between major depression and anxiety might be particularly strong in persons with a history of migraine has been reported,^{2,4,28} suggesting that in persons with migraine, depression might be characterized by prominent anxious features. Systematic examination of the phenomenology of major depression in patients with migraine would be illuminating.

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