

# Mental Disorders and the Incidence of Migraine Headaches in a Community Sample

## Results From the Baltimore Epidemiologic Catchment Area Follow-up Study

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**Background:** The cross-sectional relation between migraine headaches and affective disorders has been demonstrated in studies of clinical and community populations. Few studies have investigated the prospective relation between psychiatric disorders and migraine headaches.

**Methods:** A prospective follow-up of the Baltimore, Md, cohort of the Epidemiologic Catchment Area Study assessed psychopathologic features in 1981 and again between 1993 and 1996. Interviews included a history of headaches at baseline and self-reported assessment of migraine headaches at follow-up. Risk estimates for incident migraine headaches by 1981 demographic variables and psychopathologic features were calculated. The cross-sectional association between prevalent migraine and lifetime psychiatric diagnoses was estimated.

**Results:** In the at-risk population of 1343, there were 118 incident cases of migraine headaches. The age- and sex-specific incident rates of migraine headaches fol-

lowed the expected patterns, with younger age and female sex identified as risk factors. In cross-sectional analyses, major depression (odds ratio, 3.14; 95% confidence interval, 2.03-4.84) and panic disorder (odds ratio, 5.09; 95% confidence interval, 2.65-9.79) had the strongest associations, and alcohol and other substance abuse were not associated. In logistic regression models including age, sex, and psychiatric illness in 1981, only phobia was predictive of incident migraines (odds ratio, 1.70; 95% confidence interval, 1.11-2.58). Affective disorders were not predictive of incident migraine headaches. Including a history of tricyclic antidepressant use did not change the results.

**Conclusions:** There is a strong cross-sectional relation between affective disorders and migraine headaches in this cohort. However, there is no association between antecedent affective disorders and incident migraine headaches in this population-based prospective study.

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SEVERAL STUDIES<sup>1-4</sup> have demonstrated the cross-sectional relation between psychopathologic features and migraine headache in community samples. While the association between psychiatric disorders and migraine headaches may or may not reflect a causal one, a greater understanding of these specific relations may ultimately contribute to our understanding of the underlying etiologies of both conditions. An association between migraine headaches and the neurotransmitter serotonin and the emerging understanding of serotonin's importance in several psychiatric conditions makes this association more intriguing.<sup>5</sup>

There have been few studies,<sup>6-9</sup> however, that have examined the temporal relation between specific psychiatric disorders and migraine headaches. Associations between migraine headache and affective disorders, anxiety disorders, substance abuse disorders, and suicide attempts have

been reported.<sup>2,6-10</sup> In a prospective study of young adults from Michigan, Breslau and collaborators<sup>8</sup> found a bidirectional relation between migraine and major depression. They concluded that their results favored a "shared mechanism" etiologic explanation rather than depression simply being a biological and psychological response to migraine. In a recently published study, Breslau and collaborators<sup>9</sup> replicated the finding of a bidirectional association between major depression and migraine and reported that major depression did not predict an increase in the incidence of other severe headache types. These findings support a specific relation between depression and migraine headaches, with psychiatric conditions as potential risk factors for incident migraines.

The Baltimore Epidemiologic Catchment Area Follow-up Study has detailed information concerning psychopathologic features from an initial interview in

## SUBJECTS AND METHODS

### STUDY POPULATION

The Epidemiologic Catchment Area Program estimated the incidence and prevalence of psychiatric disorders for more than 20000 persons in population samples from 5 cities in the United States. The original sample from Baltimore, Md, included 3481 individuals selected by probability sampling methods from 3 catchment areas in East Baltimore. The details of the study design have been described in detail.<sup>11-13</sup> For the follow-up study in Baltimore, the original cohort of household respondents was traced. Of the original number, 848 had died (24% of the cohort), 415 were not located (16% of survivors), 298 refused to participate in the follow-up study (13% of those located), and 1920 were reinterviewed between 1993 and 1996 (73% of the survivors of the original cohort). The details of the follow-up study and the tracing process have been described previously.<sup>14-16</sup> There were no significant differences between the survivors of the original cohort and the follow-up group by age, sex, or psychiatric diagnoses in 1981.<sup>16</sup> For these analyses, weights to recreate the original Epidemiologic Catchment Area sample were not used.

### ASSESSMENT OF MENTAL DISORDERS

In the initial interview in 1981 and the follow-up between 1993 and 1996, the National Institute of Mental Health Diagnostic Interview Schedule was the instrument used to make psychiatric diagnoses.<sup>17</sup> This instrument consists of a highly structured interview administered by specially trained lay interviewers. For each disorder, a series of detailed, primarily "yes-no" questions are asked. The questions follow the structure of the diagnostic criteria as outlined by *DSM-III*<sup>18</sup> for the first interview and *DSM-III* and *DSM-III-R*<sup>19</sup> for the follow-up. Based on the responses to the questions, a computer algorithm generates diagnostic

categories. The Diagnostic Interview Schedule has been used in numerous studies of psychopathologic features and has established reliability and validity.<sup>17</sup> For each of the diagnostic categories, there is also information regarding the onset and recency of symptoms. For the cross-sectional analyses, a "lifetime" category is used, including those individuals who met criteria at sometime in their life before the interview between 1993 and 1996. For consistency, *DSM-III*-based diagnoses are used for the cross-sectional and prospective analyses. For the prospective analyses, a lifetime category is also used, including those meeting criteria before the interview in 1981. These variables allow for analyses testing models in which antecedent psychopathologic features are a potential risk factor for incident migraine headaches. Detailed demographic information was collected during the initial interview and at the time of the follow-up interview.

### MIGRAINE HEADACHES

Participants were asked detailed questions about their physical health. In 1981, each respondent was asked: Have you ever had a lot of trouble with headaches? If they had a positive response, they were then asked if they took medication or saw a physician for the headaches, and how recently the headache occurred. A positive response to this general headache question was used as a nonspecific, sensitive screening question to establish the at-risk study sample for estimates of incidence of migraine headaches in the study sample on follow-up. The "at-risk" population included only those individuals who had a negative response to the headache question in 1981. Presumably this excluded some individuals without migraine headaches who may have been at risk, resulting in a conservative estimate of the incidence of migraine headaches.

The interview used in the follow-up study included detailed questions about headache symptoms based on the

1981 and detailed information about headache symptoms and psychopathologic features from follow-up interviews conducted between 1993 and 1996. This prospective study of the original Baltimore Epidemiologic Catchment Area cohort provides a data set permitting estimates of incidence and prevalence of migraine headaches in the study population. Given the extensive data collected at baseline about antecedent psychopathologic features and demographic information, analysis of this data can also identify risk factors for incident, adult-onset, migraine headaches. We specifically examine depression and other psychiatric disorders as potential predictors of incident migraine headaches.

## RESULTS

There were 1920 individuals interviewed in the follow-up study. This group excluded the 362 individuals who were not at risk since they reported headaches in 1981. Also excluded from the at-risk population were 215 individuals who had incomplete or missing information

regarding headache or migraine diagnosis. This group includes many elderly respondents who had a shortened version of the interview or an informant interview. Following these exclusions, 1343 participants made up the study sample for the incidence of migraines. There were 118 incident cases of migraine headaches in the population at risk. The cumulative incidence of migraine headaches (with or without aura) was 8.8% (**Table 1**). The overall incidence estimate was higher for migraine without aura compared with migraine with aura (Table 1). For all 3 migraine classifications, the incidence rates were higher for women for every age group. The youngest age group, aged 18 to 29 years in 1981, had the highest rates for migraine without aura and the combination category. This pattern was also seen with women but not men in the migraine with aura category.

The at-risk population was divided into the 118 incident cases of migraine headaches (with or without aura) and the 1225 nonmigraine controls. The association of demographic factors from 1981, age, sex, race, educational status, marital status, and household income with

International Headache Society diagnostic criteria for migraine headaches.<sup>20</sup> A series of questions based on the criteria for migraine headaches were asked if the participant had a positive response to an initial question about severe headache symptoms. These questions inquired about classic migraine symptoms such as unilateral pain, pounding sensations, photophobia, phonophobia, an inability to carry on with usual activities, and visual symptoms. Computer-generated diagnostic algorithms were written based on the International Headache Society criteria, to be outlined.

The same initial screening question was used as the first criterion for migraine without aura and migraine with aura: Was there ever a period when you had severe headaches that lasted more than 4 hours? If the respondent had a positive response, the more detailed questions were asked. The criteria for migraine without aura were as follows: (1) a positive response to the screening question; (2) unilateral, pounding, or pulsating pain or worsening of pain with physical activity; (3) being unable to carry on with usual daily activities; and (4) nausea, vomiting, or photophobia and phonophobia.

There were 2 major criteria for the case definition of migraine with aura: (1) a positive response to the initial screening question and (2) reporting at least 1 aural symptom either before the headache or before and during the headache. If the aural symptoms were reported to occur only during the headache, the case definition was not satisfied. Aural symptoms that qualified for the case definition were as follows: seeing things like spots, lines, flashing lights, or "heat waves"; a complete or partial loss of vision; other changes in vision; numbness or tingling in any part of the body or face; and weakness or clumsiness of the arms or legs.

Incidence rates were estimated for migraine without aura and migraine with aura. For the remainder of the analyses, migraine was defined as either cases of migraine without aura or cases of migraine with aura.

## DATA ANALYSES

Incidence rates were calculated for the population at risk. The respondents with a history of headaches in 1981 were excluded from the total sample as not at risk for incident migraines. The respondents with missing information were also excluded from the calculated rates. The cumulative incidence rates of migraine headaches between 1981 and 1996 were calculated for the at-risk sample (n=1343) for migraine without aura, migraine with aura, and the combined definition of migraine. Age- and sex-specific incidence rates were also calculated.

A case-control analysis comparing cases of incident migraine headaches with the nonmigraine controls was conducted to calculate risk estimates for migraine headaches by 1981 demographic variables and psychopathologic features. Crude odds ratios (ORs) and adjusted ORs were calculated with 95% confidence limits. Adjusted ORs and 95% confidence intervals were calculated for each demographic variable using a logistic regression model that had incident migraine as the outcome variable and included all of the demographic variables in the model. The cross-sectional association between prevalent migraine and psychopathologic features was investigated by calculating the ORs for lifetime psychiatric diagnoses, as diagnosed at follow-up, and lifetime migraine. For this cross-sectional analysis, those with a history of headaches were not excluded (n=1729); the 191 participants with incomplete information were excluded.

The temporal relation between psychopathologic features and migraine was then tested in the at-risk sample for incident migraine (n=1343). The significant factors from the demographic analysis were included in logistic regression models that investigated the relation between antecedent psychiatric disorders and incident migraine headaches to control for potential confounding effects. A series of logistic regression models were tested. In the first model, each regression included age, sex, and psychiatric diagnostic category. The second model also included history of tricyclic antidepressant use.

incident migraines was calculated (**Table 2**). After adjustment for all the variables included in the model, only female sex and the youngest age group were risk factors for increased odds of incident migraine headaches. Women compared with men had an adjusted OR of 4.58 that was statistically significant. The youngest age group (those aged 18-29 years) had an adjusted OR of 4.52 that was also significant. As they were the demographic variables with significant associations with incident migraine, age and sex were included in the models with antecedent psychopathologic features.

In cross-sectional analyses of lifetime *DSM-III*-based psychiatric diagnoses and prevalent migraine headaches, major depression and panic disorder had the strongest associations (**Table 3**). These associations remained significant after adjusting for age and sex. The phobias—agoraphobia and simple and social phobias—also had a significant but less robust association. The association between migraine headaches and simple phobia and agoraphobia remained significant following adjustment, but the association with social phobia did not.

A series of logistic regression models estimated the OR for various categories of antecedent psychopathologic features as a risk factor for developing migraine headaches during the follow-up interval. **Table 4** outlines the model components and the adjusted ORs and 95% confidence intervals for antecedent psychiatric disorders, age, and sex. The adjusted OR and 95% confidence intervals for age and sex are similar for each model. In the 2 models, there was no change in the level of significance for sex from  $P < .001$ . The age groups 18 to 29 years and 30 to 44 years also had no change in statistical significance from  $P < .001$ . The only specific psychiatric disorder that has a significant increase in odds for incident migraine headaches associated with it is phobia. The OR is 1.70, indicating a modest increase in the odds of developing migraines for those with a history of phobia at the time of the initial interview. Given the strong cross-sectional associations between migraines and affective disorders reported in the literature, which was also found in our sample, a combination category for "any affective disorder" was also tested in a separate model with the

**Table 1. Cumulative Incidence of Migraine Headaches (Rate per 100) Between 1981 and 1994 by Age, Sex, and Migraine Type in the Baltimore ECA Follow-up Study\***

Age in 1981, y	No. of Subjects	Migraine Type†		
		With Aura	Without Aura	Either With or Without Aura‡
<b>Men</b>				
18-29	223	1.3	6.3	7.2
30-44	167	2.4	1.2	2.4
≥45	178	0.6	0.0	0.6
<b>Total</b>	<b>568</b>	1.4	2.8	3.7
<b>Women</b>				
18-29	246	8.1	18.3	19.9
30-44	224	7.6	12.1	14.7
≥45	305	3.0	3.3	4.9
<b>Total</b>	<b>775</b>	5.9	10.6	12.5
<b>Total (men and women)</b>				
18-29	<b>469</b>	4.9	12.6	13.9
30-44	<b>391</b>	5.4	7.4	9.5
≥45	<b>483</b>	2.1	2.1	3.3
<b>Total</b>	<b>1343</b>	4.0	7.3	8.8

\*There were 362 subjects not at risk, and data were missing for 215 subjects. ECA indicates Epidemiologic Catchment Area.

†Data are given as percentage of subjects.

‡Categories of migraine with aura and migraine without aura are not mutually exclusive; the combination category includes all participants with migraine.

age- and sex-adjusted OR being 0.97 (95% confidence interval, 0.44-2.12). A combination category of “any anxiety disorder” had results parallel to those for phobias, which constituted most of the category (data not shown). Including a history of tricyclic antidepressant use in the second model to control for the potential prophylactic benefit of tricyclic antidepressants for migraine headaches resulted in almost identical results (Table 4).

#### COMMENT

The age- and sex-specific incidence rates of migraine headaches reported in Table 1 add to the limited literature on adult-onset migraine.<sup>21,22</sup> These estimates of incidence followed the expected age and sex patterns: female sex and younger age have been previously identified as risk factors for migraine headaches in numerous studies.<sup>23-27</sup>

We replicated previous reports<sup>1-4</sup> of a cross-sectional relation between migraine headaches and psychiatric disorders. The strongest relations with migraine headache were found with the anxiety and affective disorders. These results confirm similar associations between anxiety and mood disorders found in previous studies.<sup>2,3,6-8,28,29</sup> Unlike the Michigan study that also demonstrated an association between migraine and alcohol or other drug abuse,<sup>3,6</sup> we did not observe a cross-sectional relation between substance abuse disorders and prevalent migraine.

The most intriguing result from this analysis is the lack of an association between antecedent affective disorder and incident migraine headaches, given the demonstrated cross-sectional relation between migraines and affective disorders. This differs from the finding of Breslau et al<sup>8</sup> of a bidirectional relation, with migraine predicting incident depression and depression predicting incident migraine. However, the cohort studied by Breslau et al was significantly younger and closer in age to the age of peak incidence of migraine. The Zurich, Swit-

zerland, and Michigan studies found that the onset of migraine headaches usually preceded the onset of affective disorders when both conditions were present.<sup>2,7,8,28</sup> This temporal relation would be consistent with our results of a cross-sectional but not predictive relation between affective disorders and migraine.

One of the limitations of this study is a lack of detailed information about headaches from the 1981 interview. We made the decision to exclude all individuals with a positive response to the broad headache question in 1981 to estimate the incidence of migraine conservatively. This decision likely excluded some persons who did not meet the criteria for migraine in 1981 but who might have developed migraine during the follow-up period. It may be that those with nonspecific headaches are at higher risk for affective disorders and migraine and that this exclusion could alter the association. The relation between migraine and affective disorders is likely to be a complex one, with possible interaction during the emergence of psychiatric and headache symptoms. Another limitation is the self-report of headache symptoms at follow-up without direct clinical assessment. Because the initial assessment of headaches was limited, we cannot test the bidirectional hypothesis. The older age of our cohort also restricted our study. As members of the cohort were at least aged 18 years in 1981, we could not include in this analysis those with the incidence of migraine during their childhood or teenage years. Our study's focus on the incidence of migraine in a sample composed only of adults may demonstrate that the associations between psychiatric disorders and adult-onset migraine differ from the associations seen with earlier-onset migraine. There may be differences in the pathophysiological features of migraine for adult onset vs childhood onset that are underlying the differences in association seen in different studies.

The large community cohort studied is also a major strength of our study. The prospective design of the

**Table 2. Baseline Demographic Characteristics of Cases With Incident Migraine and Controls With No Headache History in the Baltimore ECA Follow-Up Study (1981-1994)\***

Demographic Characteristics in 1981	Cases (n = 118)	Controls (n = 1225)	Adjusted Odds Ratio (95% Confidence Interval)†
Age in 1981, y			
18-29	65	404	4.52 (2.20-9.31)‡
30-44	37	354	2.91 (1.43-5.92)‡
≥45	16	467	1.00 (. . .)
Sex			
Female	97	678	4.58 (2.72-7.71)‡
Male	21	547	1.00 (. . .)
Race			
White	76	778	0.64 (0.39-1.04)
Nonwhite	42	447	1.00 (. . .)
Educational level completed			
≤8th grade	9	216	0.48 (0.18-1.31)
Grades 9-11	25	301	0.71 (0.38-1.32)
Grade 12	44	408	0.75 (0.46-1.23)
College	40	300	1.00 (. . .)
Marital status§			
Married	47	565	1.00 (. . .)
Widowed	5	123	0.79 (0.46-1.37)
Separated or divorced	23	205	0.67 (0.20-2.22)
Never married	43	331	1.10 (0.60-2.04)
Household income, \$\$			
<4999	15	142	0.90 (0.33-2.45)
5000-9999	14	188	0.74 (0.29-1.89)
10 000-14 999	21	202	0.87 (0.36-2.08)
15 000-19 999	15	166	0.85 (0.35-2.05)
20 000-34 999	34	327	1.01 (0.46-2.21)
≥35 000	10	90	1.00 (. . .)

\* There were 362 subjects not at risk, and data were missing for 215 subjects (sample total = 1920). ECA indicates Epidemiologic Catchment Area; ellipses, data not applicable.

† The adjusted odds ratios were from logistic regression models containing all demographic variables.

‡ P < .001.

§ Missing data resulted in a smaller number available for the analyses.

**Table 3. Cross-Sectional Associations Between Prevalent Migraine Headaches and Lifetime Psychiatric Diagnoses: 1994 Baltimore ECA Follow-up Study of 1729 Subjects\***

DSM-III Diagnosis at Follow-up in 1994	Association With Migraine Headaches	
	Odds Ratios (95% Confidence Interval)	Odds Ratios (95% Confidence Interval) Adjusted for Age and Sex
Major depression	3.14 (2.03-4.84)†	2.25 (1.43-3.54)†
Obsessive compulsive disorder	1.55 (0.73-3.26)	1.32 (0.61-2.87)
Panic disorder	5.09 (2.65-9.79)†	3.40 (1.72-6.70)†
Phobia	1.78 (1.35-2.35)†	1.43 (1.07-1.91)‡
Agoraphobia	2.50 (1.79-3.50)†	1.88 (1.33-2.67)†
Simple phobia	1.66 (1.27-2.18)†	1.35 (1.02-1.79)‡
Social phobia	1.45 (1.05-2.01)‡	1.27 (0.91-1.78)
Alcohol and/or other drug abuse	0.80 (0.55-1.16)	1.05 (0.70-1.57)

\* ECA indicates Epidemiologic Catchment Area.

† P < .001.

‡ P < .05.

study and baseline information about headaches allowed us to estimate the incidence of migraine and add to the limited literature regarding incidence. The structured psychiatric diagnoses at baseline and follow-up are another strength of this study's design. The prospective

design and nearly 13 years of follow-up facilitated studying the temporal relations between migraine headaches and psychiatric illnesses. Finally, the extensive information about history of previous use of psychotropic medications permitted adjustment for a history of tricyclic antidepressant use. As tricyclic antidepressants are an effective prophylactic medication commonly used to prevent recurrence of migraine, their use to treat an antecedent depression might have affected the incidence of migraine. As outlined in Table 4, a history of tricyclic antidepressant use was not masking the association between affective illness and migraine headaches.

One explanation for the strong cross-sectional association but the lack of a predictive association is the typical course and ages at onset of migraine headaches and psychiatric disorders—the mean age at onset for migraine is earlier than that for depression and other affective disorders. The Zurich study's finding that anxiety disorders typically precede the incidence of migraine<sup>2,7,28</sup> is consistent with our finding that antecedent phobias predict incident migraine headaches. Another possible explanation is that migraine and affective disorder are at increased risk due to a third factor. If migraine and affective disorder had a common risk factor, they might have an emergence of symptoms during a similar period rather than one increasing the risk for the other. Candidates for this common risk factor include alterations in

**Table 4. Logistic Regression Models: Age, Sex, and Antecedent Psychopathologic Features as Predictors of Incident Migraine Headaches in the Baltimore ECA Follow-up Study of 1343 Subjects (1981-1994)\***

DIS or <i>DSM-III</i> Psychiatric Diagnosis in 1981	Adjusted Odds Ratio (95% Confidence Interval)	
	Model 1†	Model 2‡
Any affective disorder	1.00 (0.46-2.18)	0.97 (0.44-2.12)
Major depression	0.68 (0.24-1.97)	0.65 (0.22-1.90)
Dysthymia	1.56 (0.44-5.57)	1.50 (0.42-5.39)
Obsessive compulsive disorder	1.35 (0.50-3.64)	1.33 (0.49-3.60)
Phobia	1.70 (1.11-2.58)§	1.70 (1.12-2.60)§
Panic disorder	1.11 (0.13-9.36)	1.08 (0.13-9.05)
Alcohol and/or other drug abuse	1.14 (0.64-2.02)	1.13 (0.64-2.02)
Any DIS or <i>DMS-III</i> disorder except phobia	0.92 (0.56-1.49)	0.90 (0.55-1.48)
Any DIS or <i>DSM-III</i> disorder	1.37 (0.92-2.03)	1.37 (0.92-2.04)

\*ECA indicates Epidemiologic Catchment Area; DIS, Diagnostic Interview Schedule.

†Includes age, sex, and one category of psychiatric illness in 1981. The odds ratio for age 18 to 29 years is approximately 5.5 (range, 5.36-5.58); for age 30 to 44 years, approximately 3.3 (range, 3.16-3.36); and for female sex, approximately 4.3 (range, 4.01-4.42) ( $P < .001$  for all).

‡Includes age, sex, history of tricyclic antidepressant use, and one category of psychiatric illness in 1981. The odds ratio for age 18 to 29 years is approximately 5.5 (range, 5.31-5.56); for age 30 to 44 years, approximately 3.3 (range, 3.18-3.37); and for female sex, approximately 4.3 (range, 4.01-4.42) ( $P < .001$  for all).

§ $P = .01$ .

the brain's serotonergic pathways that have been linked with migraine and affective disorders. Further research focusing on the relation between migraine and affective disorders and the elements of their underlying neurophysiological features, which are potentially shared, will hopefully lead to a better understanding of each condition's etiology and ultimately more rational and effective treatments for both.

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