Headache
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ISSN 0017-8748
doi: 10.1111/j.1526-4610.2010.01705.x
Published by Wiley Periodicals, Inc.

Research Submission

The Shared Genetics of Migraine and Anxious Depression

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Objectives.—To investigate (1) whether shared genetic factors influence migraine and anxious depression; (2) whether the genetic architecture of migraine depends on anxious depression; (3) whether the association between migraine and anxious depression is causal.

Background.—Migraine and anxious depression frequently occur together, but little is known about the mechanisms causing this association.

Methods.—A twin study was conducted to model the genetic architecture of migraine and anxious depression and the covariance between them. Anxious depression was also added to the model as a moderator variable to examine whether anxious depression affects the genetic architecture of migraine. Causal models were explored with the co-twin control method.

Results.—Modest but significant phenotypic (rP = 0.28), genetic (rG = 0.30), and nonshared environmental (rE = 0.26) correlations were found between the 2 traits. Interestingly, the heritability of migraine depended on the level of anxious depression: the higher the anxious depression score, the lower the relative contribution of genetic factors to the individual differences in migraine susceptibility. The observed risk patterns in discordant twins are most consistent with a bidirectional causal relationship.

Conclusions.—These findings confirm the genetic association between migraine and anxious depression and are consistent with a syndromic association between the 2 traits. This highlights the importance of taking comorbidity into account in genetic studies of migraine, especially in the context of selection for large-scale genotyping efforts. Genetic studies may be most effective when migraine with and without comorbid anxious depression are treated as separate phenotypes.

Key words: migraine, depression, genetics, comorbidity, causality

Abbreviations: BIC Bayes Information Criterion, DZ dizygotic, LCA latent class analysis, MZ monozygotic, OR odds ratio

(*Headache* 2010;50:1549-1560)

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Accepted for publication April 12, 2010.

Conflict of Interest: No conflict.

Financial support: This study was supported by grants from The Netherlands Organisation for Scientific Research, and the Centre for Medical Systems Biology (NWO-CMSB), Spinozapremie (NWO/SPI 56-464-14192), Borderline Personality Disorder Research Foundation, genome-wide analyses of European twin and population cohorts (EU/QLRT-2001-01254), resolving cause and effect in the association between regular exercise and psychological well-being (NWO-MW 904-61-19). Statistical analyses were carried out on the Genetic Cluster Computer (http://www.geneticcluster.org; NWO 480-05-003).

Migraine and depression consistently show an association, which may be explained by a shared etiology, for instance, genetic risk factors. Several authors have suggested that disturbances in the serotonergic and dopaminergic systems, involved in both migraine and depression, might explain the association between the 2 traits.[1,2]

Two recent studies investigated the association between migraine and depression and found that the 2 traits were genetically correlated.[3,4] This may reflect the existence of genetic risk factors that can cause migraine as well as depression (pleiotropy). Alternatively, if there is a causal relationship between 2 traits, genetic factors contributing to the first trait will also explain variance in the second trait. Thus, a causal relationship is also consistent with a genetic correlation. Whether traits are related causally or through an underlying shared etiology can be examined using twin and family data.[5,6]

In the present study, we investigated the shared genetics of migraine and anxious depression in 3 different ways. A twin design was used to (1) test whether the previously reported genetic correlation between migraine and depression could be replicated in migraine and anxious depression data from a large number of Dutch twins; (2) investigate whether the genetic architecture of migraine was the same in individuals with high and low anxious depression scores. Finally, to address the question of causality, the co-twin control method[3] was applied to investigate whether the association between migraine and anxious depression is more likely explained by a causal model or a shared underlying etiology.

METHODS

Subjects.—The participants in this study were volunteer members of the Netherlands Twin Registry (NTR), based at the department of Biological Psychology of the VU University in Amsterdam. NTR participants receive mailed questionnaires every 2 to 3 years, in the context of an ongoing study of health, lifestyle, and personality. The migraine and anxious depression data used in this study were collected in the 2002 and 2004 surveys. When a participant answered the headache section in both surveys, the most recent (2004) survey was used. Data collection procedures are described in detail elsewhere.[7,8] The study was approved by the Central Ethics Committee on Research Involving Human Subjects of the VU University Medical Center, Amsterdam. All subjects provided written informed consent.

The analysis performed to assign affection status for migraine to each individual was based on the largest possible sample with migraine data available, including twins, parents, singleton siblings, and spouses (N = 14,904, including 12,303 NTR and 2601 NESDA[4] participants). Further analyses were based on the data of twins only (N = 5535; 2072 complete pairs and 1391 individuals from incomplete pairs). Migraine data were available for all 5535 individuals; 4320 twins also provided data on anxious depression, resulting in a total of 1491 complete twin pairs with information on both migraine and anxious depression (223 monozygotic [MZ] male, 100 dizygotic [DZ] male, 602 MZ female, 286 DZ female, and 280 DZ opposite sex pairs). In total, the sample consisted of 1774 (32%) male and 3761 (68%) female participants and the mean age was 34.33 years (SD = 11.35, range 14-86 years).

Measures.—The subjects completed a questionnaire that included items relating to the diagnostic criteria for migraine of the International Headache Society[5] (IHS) (see Table 1). Migraine status was assigned to each subject based on a latent class analysis (LCA),[6,7] which empirically classifies individuals according to their pattern of reported migraine symptoms. The advantage of using LCA to classify migraine patients is that it allows the classification of not only severe migraine patients, but also the milder cases.[8,9] This is particularly important in population-based samples, which are unselected with respect to migraine status. Although mildly affected migraine patients may not qualify for a clinical diagnosis of migraine, they are expected to carry a certain genetic risk of migraine, and are therefore informative in genetic studies. Discarding their data, or treating them as unaffected will lead to a severe reduction in the power to detect genetic effects. LCA has been successfully applied in several previous genetic studies of migraine and has been described in more detail elsewhere.[8-11] For simplicity, LCA-derived migrainous headache will be referred to as

Table 1.—Headache Questions Included in the Surveys and Correspondence to IHS Diagnostic Criteria for Migraine

Item in survey	Code	Description
Do you ever experience headache attacks, for instance migraine? (yes/no)		Screening question
How often do you have these headache attacks?†	A	≥5 episodes
How long do these headache attacks usually last?	B	4-72 hours
The headache is usually pounding or stabbing (yes/no)	C2	Pulsating quality
How intense is the headache during most attacks? (mild/moderate/severe)	C3	Moderate or severe pain intensity
During a headache attack, do you experience: (yes/no)		
Aggravation of headache by physical activity?	C4	Aggravation by physical activity
Nausea or vomiting?	D1	Nausea and/or vomiting
Aversion of light, sound, or smell?‡	D2	Photo- and phonophobia
Partial loss of vision, seeing flashes of light or (zigzag) patterns?	Aura	Visual aura

†An attack frequency of "several times a year" or more was assumed to be equivalent to "≥5 episodes."
‡The official criteria do not include osmophobia and require both photo- and phonophobia; however, from these data, it was not possible to determine whether both were present.
IHS = International Headache Society.

"migraine" throughout the remainder of the paper. LCA was performed in Latent Gold 4.0 (Statistical Innovations Inc., Belmont, MA, USA). The correct number of classes was determined based on the Bayes Information Criterion (BIC),[12] with a lower BIC indicating a better fit to the data.

The anxious depression measure consisted of a factor score based on several measures of anxiety, depression, and neuroticism. These 3 traits are strongly correlated, and mostly affected by the same genetic factors. The factor score was calculated using an algorithm developed in a previous twin study on anxious depression.[13] This score was recoded into quartiles, with quartile 1 indicating a low anxious depression score and quartile 4 indicating a high score.

Genetic Modeling.—In the classical twin study, the resemblance between twins is used to estimate to what extent a trait is influenced by additive genetic factors (A), shared (or common) environment (C), and nonshared environment (E). MZ twins share 100% of their segregating genes, whereas DZ twins share on average 50%. Differences between MZ twins reflect E. Greater resemblance in MZ compared with DZ twins reflects genetic influences, with an MZ correlation (rMZ) equal to twice the DZ correlation (rDZ) indicating A, and an rMZ, which is less than twice the rDZ indicating A and C. Based on these principles, the total variance in a trait can be decomposed into variance because of A, C, and E. Estimation of the relative contributions of A, C, and E can be accomplished with structural equation modeling. Figure 1 shows a path diagram of the model tested here. As there was no evidence for shared environmental effects based on the observed twin correlations or the literature,[14,15] an AE model was tested for both traits.

To investigate whether the genetic and environmental factors influencing migraine and anxious depression were correlated, a bivariate genetic model was tested (Fig. 1). This model included genetic and environmental factors for both traits, partly unique to each trait (the a_{11}, a_{22} e_{11}, and e_{22} paths), and partly shared (a_{21} and e_{21}). The shared part represents the covariance between the 2 traits, which can be decomposed into covariance explained by genetic and environmental factors. This is performed based on the cross-trait cross-twin correlations (ie, the correlation between one trait in the first twin and the other trait in the second twin). The cross-twin cross-trait correlations are interpreted in the same way as the within-trait twin correlations, with correlations higher in MZ than DZ twins indicating genetic factors influencing both traits. By standardizing the parts of the covariance because of A and E, genetic and environmental correlations can be calculated. The significance of these correlations was tested by dropping the a_{21} and e_{21} paths from the model and comparing the fit of the restricted and full models.

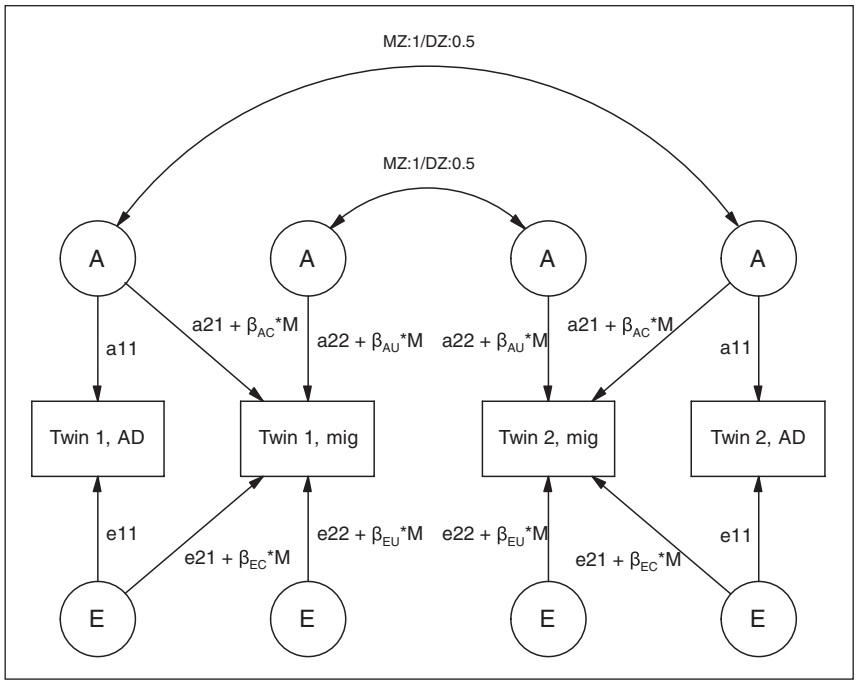

Fig 1.—The bivariate moderator model. The genetic (A) and nonshared environmental (E) factors influencing migraine are moderated by AD (M). The a and e path coefficients represent the genetic and nonshared environmental influences on migraine only (path coefficients a_{22} and e_{22}, respectively) and the influences on both migraine and AD (path coefficients a_{21} and e_{21}). The regression betas represent the moderation of the genetic and nonshared environmental effects by AD. Parameters β_{AU} and β_{AC} represent the effect of AD on the genetic factors unique to migraine, and the genetic factors common to migraine and AD, respectively. Similarly, β_{EU} and β_{EC} represent the effect of AD on the nonshared environmental factors. AD = anxious depression, mig = migraine.

A liability threshold model was tested for both migraine and anxious depression. A threshold model assumes that the observed categorical data (eg, a variable with values 1-4 indicating severity of migraine) are an imperfect measurement of an underlying normal distribution of liability with a mean of zero and a variance of 1. This distribution is divided into discrete categories by 1 or more threshold values, expressed as *Z*-scores. The area under the curve between 2 thresholds represents the prevalence of each category. The categorized anxious depression variable was already adjusted for sex; therefore, the thresholds for both sexes were equated in the model. Migraine, as expected, had a higher prevalence in females. Thus, the thresholds for migraine were estimated separately for males and females.

To test whether the heritability of migraine depends on anxious depression, anxious depression was specified as a moderator of the path coefficients a_{21} and e_{21} (which represent the variance shared by migraine and depression) and a_{22} and e_{22} (which represent the variance unique to migraine). In other words, the effects of the genetic and environmental factors affecting migraine were allowed to vary depending on depression status. The significance of the moderation effect was evaluated by dropping the beta parameters β_{AC}, β_{AU}, β_{EU}, and β_{EC} from the model and assessing the difference in model fit.

To ensure identification of the model, the total variance in a threshold model has to be constrained to one. However, in the model used here the variance of migraine depends on the value of the moderator (anxious depression). Therefore, the moderator variable was converted to a *Z*-score; the variance was constrained to be one at the mean value of the moderator, as proposed by Medland et al.[16] All genetic modeling was performed in Mx.[17]

Co-twin Control Method.—The co-twin control method[3] was applied to test the hypothesis that (1) anxious depression causes migraine; (2) migraine

causes anxious depression. In this design, an odds ratio (OR) is calculated for trait A, given the presence or absence of trait B. This is performed in 3 groups of individuals: MZ and DZ twin pairs discordant for trait B, and a case–control population sample. Thus, in the general population sample we compare the prevalence of trait A in all individuals with trait B vs all individuals without trait B. In the discordant twin samples, we compare the prevalence of A in the twins with trait B vs the co-twins without trait B.

Under a *causal* model, all 3 groups are expected to show a similarly increased prevalence of A, given the presence of B: trait B has to be present in the same individual to increase the risk of A. Therefore, the OR in all 3 groups will be larger than 1, as the individuals with trait B have a higher risk than the individuals without trait B. Under a *noncausal* model, where shared underlying genetic factors explain the association, the expectation for a general population sample is the same (OR > 1), but in MZ twins the OR is expected to be smaller, because MZ twins are exposed to the same genetic risk factors, and should therefore have the same genetic risk of trait A regardless of the presence of trait B. DZ twins will show an intermediate pattern (Fig. 2A).

For this analysis, anxious depression was dichotomized; individuals in the highest scoring quartile were treated as cases, the lowest 3 quartiles were treated as controls. A "general population" sample was obtained by randomly selecting 1 individual from each family in the NTR sample (total N = 12,303), excluding the discordant twins. The sample included 358 MZ and 418 DZ pairs discordant for anxious depression, and 454 MZ and 510 DZ pairs discordant for migraine. The general population sample consisted of 2838 unrelated individuals. ORs were calculated in SPSS 17.

RESULTS

Four classes of individuals were identified, based on the patterns of reported migraine symptoms. The 4-class LCA model provided a better fit to the data (BIC = 60,139.87) than a 3- or a 5-class model (with a BIC of 60,185.03 and 60,233.40, respectively). Figure 3 shows the pattern of symptoms in each class. The 2 most severe classes were treated as affected for migrainous headache, the remaining individuals were treated as unaffected. In the twin sample used in all subsequent analyses, 14% of the male and 35% of the female participants were classified as affected, which is comparable with the combined prevalence of migraine and probable migraine, according to IHS criteria.[18]

A clear comorbidity of migraine and depression was observed, with a migraine prevalence of 20% in the lowest anxious depression quartile and 43% in the highest scoring quartile. The phenotypic correlation between migraine and anxious depression was estimated at 0.28 (95% CI = 0.20-0.36).

Table 2 shows an overview of the correlations across twins and traits. The twin correlations for both migraine and anxious depression were clearly higher in MZ than DZ twins, reflecting genetic influences on both traits. Genetic modeling results indicated that the variance in migraine could be explained by a combination of genetic (45%) and nonshared environmental factors (55%). For anxious depression, genetic factors explained 55% and nonshared environment explained 45% of the variance.

The cross-twin cross-trait correlations were also higher in MZ than DZ twins, suggesting the correlation between migraine and anxious depression is at least partly explained by genetic influences. Most of the covariance between the 2 traits was indeed explained by shared genetic factors (54%), while nonshared environment was responsible for the remaining covariance (46%). The genetic correlation (rG) between anxious depression and migraine was estimated at 0.30 (95% CI = 0.18-0.43) while the nonshared environmental correlation (rE) was 0.26 (95% CI = 0.15-0.37). Both correlations were significant: dropping a_{21} and e_{21} from the model both resulted in a significant deterioration in model fit ($\Delta\chi^2(1) = 17.834$, $P < .001$ for a_{21}, $\Delta\chi^2(1) = 15.535$, $P < .001$ for e_{21})

The next step was to test the significance of the moderation effect of anxious depression on the heritability of migraine, by dropping the moderator betas from the model and assessing the resulting deterioration in model fit. The power to test the significance of these parameters individually was low (as reflected by confidence intervals that included zero; Table 3).

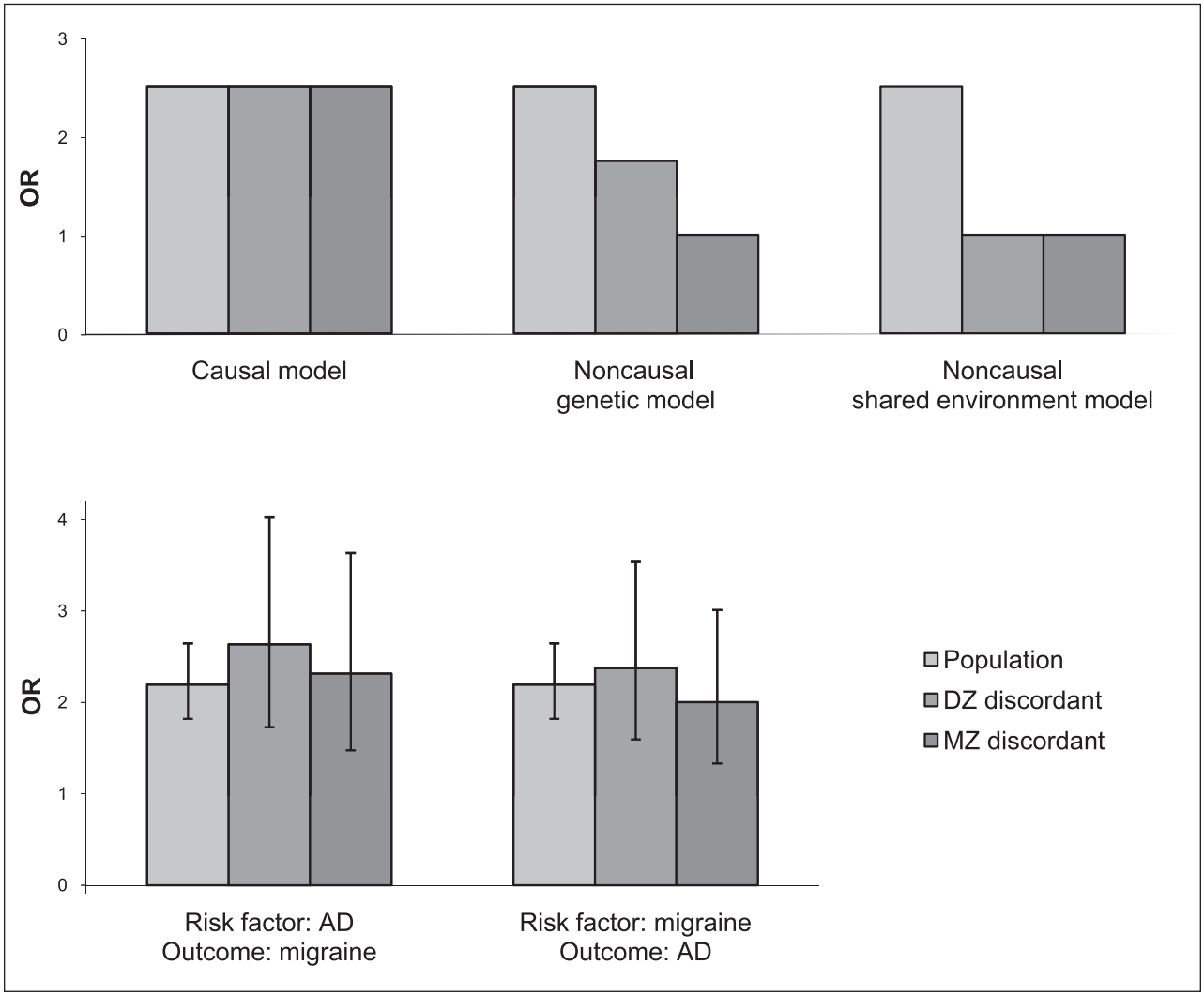

Fig 2.—(A) Expected patterns of odds ratios (OR) for general population and discordant DZ and MZ twins under the assumptions of causality and noncausality. Under the causal hypothesis, trait A and B are associated in all 3 groups. Under the noncausal hypothesis, where genetic factors explain the association, discordant MZ twins have an OR of 1, because they are genetically identical and are thus exposed to the same genetic risk factors. The DZ twins, who share on average 50% of their segregating genes, show an intermediate pattern. Finally, if the association is noncausal but explained by shared environment, all discordant twins are expected to have an OR of 1. However, in this case, this is unlikely because there is no evidence that shared environment affects migraine or depression. (B) Observed pattern of OR in general population and discordant DZ and MZ twin pairs, for both possible directions of causality between migraine and anxious depression (AD). The error bars represent the 95% confidence intervals around the ORs. In both situations, all ORs have roughly the same size for each group. This is most consistent with the causal hypothesis. DZ = dizygotic; MZ = monozygotic.

However, dropping all 4 β parameters from the model at once resulted in a significant deterioration of the model fit ($\Delta\chi^2(4) = 12.478$, $P = .014$), indicating that, overall, the moderator variable is of importance in explaining the observed data. Figure 4 shows the effect of anxious depression on the genetic and environmental factors influencing migraine. As the anxious depression score becomes higher, the relative contribution of genetic factors to the individual differences in migraine susceptibility becomes smaller. The estimated heritability of migraine was highest at a low level of anxious depression. In other words, genetic factors are most important in the absence of anxious depression.

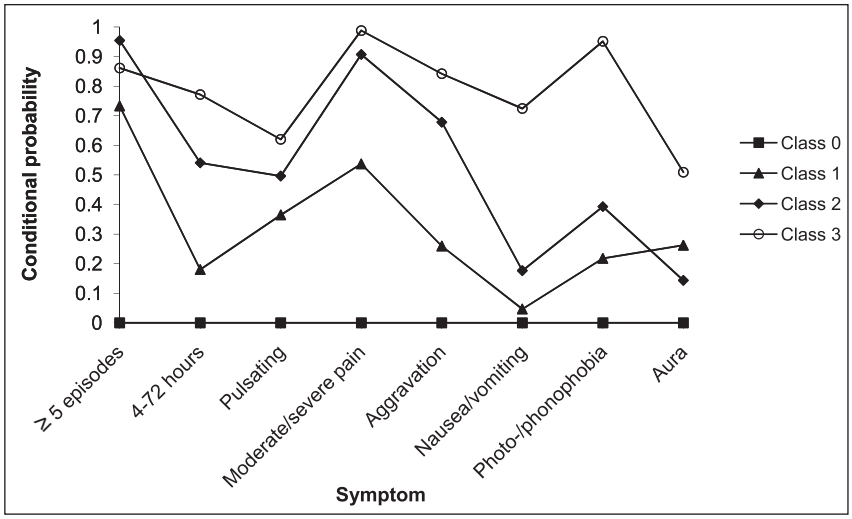

Fig 3.—Profile plot for the best fitting latent class model, showing the symptom prevalence in each of the empirically estimated classes. The migraine symptoms are on the x-axis, the y-axis shows the probability that a symptom is present given class membership.

Finally, Figure 2B shows the results of the co-twin control analysis. Under the hypothesis that anxious depression causes migraine, the ORs in the general population, discordant DZ and discordant MZ samples were 2.20 (95% CI = 1.82-2.65), 2.64 (1.73-4.02), and 2.32 (1.48-3.64), respectively. Under the hypothesis that migraine causes anxious depression, the ORs were 2.20 (1.82-2.65), 2.38 (1.60-3.54), and 2.00 (1.33-3.01), respectively. Thus, in all 3 groups, the OR was roughly the same. This was the case under both hypotheses. The 95% confidence intervals indicate that both in MZ and DZ discordant twin pairs the ORs were significantly larger than 1. The similar ORs in the 3 groups indicate that having a co-twin with depression does not increase a nondepressed individual's risk of migraine, and vice versa. These results do not support the hypothesis of pleiotropic effects, and are most consistent with a bidirectional causal relationship between migraine and anxious depression.

Table 2.—Correlation Matrices for Monozygotic and Dizygotic Twins

MZ	AD twin 1	95% CI	Mig twin 1	95% CI	AD twin 2	95% CI	Mig twin 2
AD twin 1	1.00						
Mig twin 1	0.28	(0.20-0.36)	1.00				
AD twin 2	0.55	(0.49-0.60)	0.15	(0.08-0.22)	1.00		
Mig twin 2	0.15	(0.08-0.22)	0.45	(0.35-0.55)	0.28	(0.20-0.36)	1.00
DZ	**AD twin 1**	**95% CI**	**Mig twin 1**	**95% CI**	**AD twin 2**	**95% CI**	**Mig twin 2**
AD twin 1	1.00						
Mig twin 1	0.28	(0.20-0.36)	1.00				
AD twin 2	0.27	(0.25-0.30)	0.08	(0.04-0.11)	1.00		
Mig twin 2	0.08	(0.04-0.11)	0.23	(0.18-0.27)	0.28	(0.20-0.36)	1.00

AD = anxious depression; DZ = dizygotic; Mig = migraine; MZ = monozygotic.

Table 3.—Point Estimates for the Parameters That Constitute the Variance in Migraine

Parameter	Point Estimate	95% CI
Genetic factors influencing migraine and AD (a_{21})	0.21	(0.11-0.30)
Genetic factors influencing migraine only (a_{22})	0.64	(0.56-0.71)
Unique environmental factors influencing migraine and AD (e_{21})	0.19	(0.10-0.29)
Unique environmental factors influencing migraine only (e_{22})	0.71	(0.64-0.78)
Moderation effect of AD on a_{21} (β_{AC})	0.04	(–0.05-0.13)
Moderation effect of AD on a_{22} (β_{AU})	–0.07	(–0.19-0.06)
Moderation effect of AD on e_{21} (β_{EC})	0.07	(–0.03-0.16)
Moderation effect of AD on e_{22} (β_{EU})	0.00	(–0.13-0.12)

The parameter names (between brackets) refer to the names used in Figure 1.
AD = anxious depression.

DISCUSSION

The results of this study are interesting in several aspects. First, they confirm the presence of a genetic correlation between migraine and anxious depression. This is consistent with the findings of 2 other recent studies on this topic.[19,20]

A second important outcome of this study is that migraine was more heritable when not accompanied by comorbid depression. A possible explanation for this finding would be that some neurological disturbance in the brain, associated with depression, also makes patients more vulnerable to migraine. Thus, depressed individuals without a severe genetic predisposition to migraine might still develop migraine attacks regularly. Clearly, this theory is speculative and needs further investigation; interestingly, however, various studies have shown that depressed patients report several different types of pain (headache, low back pain, abdominal pain, etc) more frequently than nondepressed individuals, suggesting that depression increases an individual's vulnerability to pain conditions.[21] It has been argued that pain

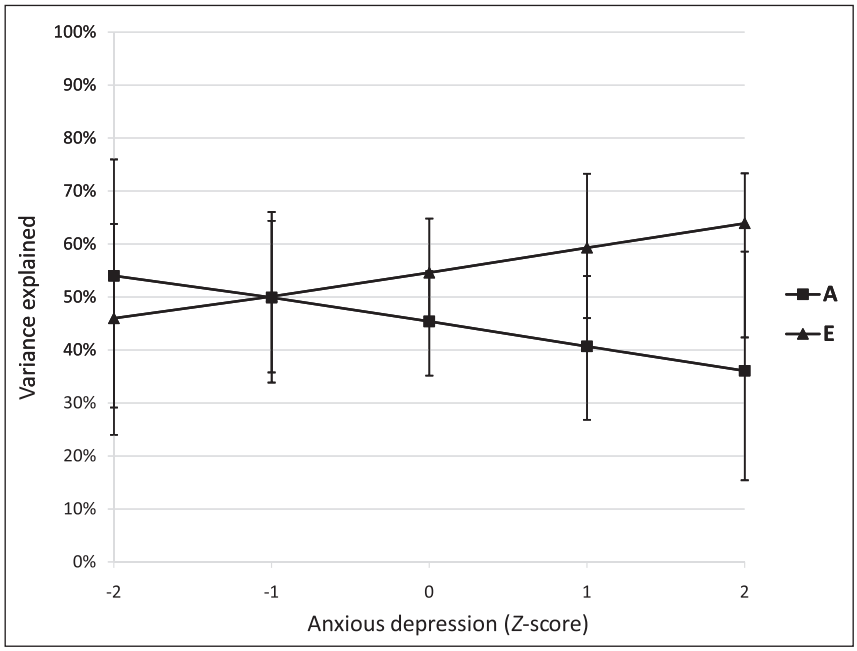

Fig 4.—The estimated heritability of migraine at different values of anxious depression, based on the bivariate moderator model. The proportion of variance in migraine explained by additive genetic factors (A) and nonshared environmental factors (E) across a range of depression scores (expressed as *Z*-scores), based on the estimates obtained from the moderator model. The higher the anxious depression score, the lower the relative contribution of genetic factors to the individual differences in migraine susceptibility. The error bars represent 95% confidence intervals.

should in fact be considered a symptom of depression.[22] It is unclear whether there is a specific association of depression with migraine (beyond the general increase in pain symptoms associated with depression), because, to date, studies of migraine and depression have not accounted for the phenomenon of comorbid pain in depressed individuals.

A third important finding is that migraine and depression are most likely causally related in 2 directions. In MZ twin pairs discordant for anxious depression, the nondepressed twin did not have an increased risk of migraine, and in MZ twin pairs discordant for migraine, the twin without migraine did not have an increased risk of anxious depression. Similar results were obtained when the analysis was restricted to female subjects only (results not shown). Males were not analyzed separately, because of the relatively low number of male discordant twin pairs.

These findings are consistent with an earlier study by Merikangas et al,[23] who reported that rates of anxiety/depression in relatives of migraineurs were only elevated in the presence of migraine in the relatives. Interestingly, a similar risk pattern can be observed in a series of prevalence diagrams published by Schur et al,[20] which showed that the co-twins of individuals with "pure" depression (ie, depression but not migraine) were not at increased risk of "pure" migraine, and vice versa. Further support for causality comes from a model proposed by de Moor et al,[24] who argued that if a relationship is causal, all factors influencing the first trait should also affect the second trait. This was indeed the case in our study: genetic and nonshared environmental factors each explained roughly half of the variance in both traits, and genetic and nonshared environmental factors each also explained approximately half of the covariance between migraine and anxious depression.

At present we can only speculate what kind of mechanism might explain a causal relationship between migraine and anxious depression. Possible explanations at the psychological level are that frequent severe migraines might cause depressive or anxious symptoms, or that depressed or anxious patients might over-report pain as a result of their mood disorder. Alternatively, there might be a syndromic association between migraine and anxious depression, as previously suggested by Merikangas et al.[23] This would indeed be consistent with the theory discussed above, that migraine might be part of the spectrum of symptoms associated with depression. If, in a subgroup of patients, comorbid migraine and depression were aspects of the same disorder, this would provide a good explanation for the pattern of risks we observed in the discordant twin pairs. This theory is especially interesting given the recent report by Stam et al[19] that part of the heritability of migraine, particularly migraine with aura, was explained by depression.

Strengths and Limitations.—Most studies on migraine comorbidity include measures of either anxiety or depression. In the present study a combined measure of "anxious depression" was used. Although this is not the same as "regular" depression, research has shown that the genetic factors influencing anxiety and depression are largely the same.[13,25] Moreover, the strong comorbidity of depression and anxiety disorders[26] makes it extremely difficult to separate the 2 disorders, and indicates that anxious depression is the most common type of depression. Thus, although some caution is in place, it seems reasonable to assume that results regarding the genetic factors influencing anxious depression can mostly be generalized to "regular" depression.

It has been reported that anxiety tends to precede migraine, and that migraine tends to precede depression in comorbid cases.[18] As we did not assess anxiety and depression separately, and measured only current migraine and anxious depression status, we do not know whether this preferential order was also present in our study population. However, it should be noted that temporal order provides limited information with respect to causality: the fact that one disorder tends to occur after the other does not prove they are causally related, nor does it exclude the possibility of pleiotropic effects. Moreover, it has been reported that the association between depression and migraine is strongest in individuals with combined depression and anxiety symptoms,[18] suggesting the anxious depression phenotype may be of particular interest in studies of migraine comorbidity.

A limitation of this study is the relatively limited power to detect the moderation of migraine heritabil-

ity by anxious depression. The effects of the moderator were small and only significant when dropped all at once. This indicates an overall moderation effect, but a larger sample is needed to determine whether genetic variance decreases, or whether nonshared environmental variance becomes larger in depressed individuals. Also, further research is needed to test whether reports on migraine symptoms are affected by mood disorders. It is possible that a tendency to overreport somatic symptoms, caused by depressed mood, would cause an overestimation of migraine prevalence in depressed individuals. This could result in a less accurate assessment of migraine status in depressed individuals, and thus in a lower heritability estimate.

To determine migraine affection status, an LCA-based classification method was used, which results in a relatively broad phenotype definition. Information on unilateral location of the headache was not available. This means that some caution should be taken in comparing this work to studies using strict clinical diagnoses of migraine. Both migraine and anxious depression were assessed based on self-report, using questionnaires. While this limits comparisons to clinical studies, this strategy also has some advantages. First, it is generally not feasible to obtain clinical diagnoses in the large numbers of subjects required for these analyses. Second, in population-based studies, including data from subclinical cases has the potential to increase the power to detect genetic effects, as we have previously shown for migraine.[9,10] The same may apply to anxious depression. In practice, using an empirical LCA-based migraine classification results in a prevalence comparable with the combined prevalence of IHS migraine and probable migraine.[27] Thus, in population-based genetic studies there are clear advantages to using broad, questionnaire-based measures, rather than strict clinical diagnoses only.

CONCLUSIONS AND IMPLICATIONS

Our finding that migraine is less heritable in severely depressed individuals has important implications for research, because it suggests that it may be important to treat migraine with and without comorbid anxiety or depression as separate phenotypes in genetic studies. This is especially worth taking into account when individuals are selected for expensive genotyping efforts. A similar conclusion follows from our findings with respect to causality. If migraine and anxious depression are causally related, "pure" migraine and migraine associated with anxious depression may not have the same etiology, which could cause considerable genetic heterogeneity.

Comorbidity with migraine has been reported for a wide range of psychiatric[18] and nonpsychiatric conditions.[28-30] Whether our findings extend to other traits beside anxious depression requires further investigation.

Finally, it is worth emphasizing the importance of further research into the nature of migraine in depressed patients. A better recognition and understanding of this phenomenon, resulting in more effective treatment and pain relief, could improve the quality of life of many individuals.

Acknowledgment: The authors would like to thank Sarah Medland for her advice on the genetic modeling.

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