

Shared Genetic Factors Underlie Migraine and Depression

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Migraine frequently co-occurs with depression. Using a large sample of Australian twin pairs, we aimed to characterize the extent to which shared genetic factors underlie these two disorders. Migraine was classified using three diagnostic measures, including self-reported migraine, the ID migraine™ screening tool, or *migraine without aura* (MO) and *migraine with aura* (MA) based on International Headache Society (IHS) diagnostic criteria. Major depressive disorder (MDD) and minor depressive disorder (MiDD) were classified using the *Diagnostic and Statistical Manual of Mental Disorders* (DSM) criteria. Univariate and bivariate twin models, with and without sex-limitation, were constructed to estimate the univariate and bivariate variance components and genetic correlation for migraine and depression. The univariate heritability of broad migraine (self-reported, ID migraine, or IHS MO/MA) and broad depression (MiDD or MDD) was estimated at 56% (95% confidence interval [CI]: 53–60%) and 42% (95% CI: 37–46%), respectively. A significant additive genetic correlation ($r_G = 0.36$, 95% CI: 0.29–0.43) and bivariate heritability ($h^2 = 5.5\%$, 95% CI: 3.6–7.8%) was observed between broad migraine and depression using the bivariate Cholesky model. Notably, both the bivariate h^2 (13.3%, 95% CI: 7.0–24.5%) and r_G (0.51, 95% CI: 0.37–0.69) estimates significantly increased when analyzing the more narrow clinically accepted diagnoses of IHS MO/MA and MDD. Our results indicate that for both broad and narrow definitions, the observed comorbidity between migraine and depression can be explained almost entirely by shared underlying genetically determined disease mechanisms.

■ **Keywords:** migraine, depression, twin study, heritability, genetic correlation, bivariate heritability

Migraine and depression are common complex disorders that share a higher than expected co-occurrence (Saraceno, 2002; Vos et al., 2012). Previous longitudinal studies (Breslau et al., 1994; Breslau et al., 2000; Breslau et al., 2003; Modgill et al., 2012; Mongini et al., 2003) identified a bidirectional association between migraine and depression, with one disorder increasing the relative risk for the other, and vice versa. However, the etiology underlying the two disorders is still poorly understood.

Previous twin and family studies consistently observed a moderate genetic effect on susceptibilities of the two disorders, with heritability (h^2) estimates of around 30–50% for both migraine (Honkasalo et al., 1995; Mulder et al., 2003; Svensson et al., 2003) and depression (Bierut et al., 1999; Duncan et al., 2014; Nes et al., 2013; Sullivan et al., 2000). Several studies also found evidence for shared genetic components between migraine and depression (Ligthart et al., 2010; Ligthart et al., 2014; Schur et al., 2009; Stam et al.,

2010). First, Schur et al. (2009) utilized bivariate structural equation modeling (SEM) in a U.S. sample of 758 monozygotic (MZ) and 306 dizygotic (DZ) female twin pairs to estimate a trait-specific heritability of 52% (95% confidence interval [CI]: 11–66%) for self-reported doctor's diagnosis of depression and 44% (95% CI: 18–55%) for self-reported doctor's diagnosis of migraine headache, and the authors estimated that 20% of the variance in depression and migraine is due to shared genetics (i.e., bivariate heritability of 20%)

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and 4% of the unique environmental component is shared. A second twin study using 223 MZ male, 100 DZ male, 602 MZ female, 286 DZ female, and 280 DZ opposite-sex Dutch twin pairs (Ligthart et al., 2010) estimated a heritability of 45% for latent class analysis (LCA)-derived migrainous headache and 55% for anxious depression — a measure consisting of a factor score based on several measures of anxiety, depression, and neuroticism — and estimated a genetic correlation (r_G) between migrainous headache and anxious depression of 0.30 (95% CI: 0.18–0.43). Additionally, a family based study in a large Dutch genetic isolate utilized International Headache Society (IHS) diagnostic criteria and reported significant heritability estimates for migraine without aura (MO) ($h^2 = 0.77$, 95% CI: 0.38–1.00), migraine with aura (MA) ($h^2 = 0.96$, 95% CI: 0.51–1.00), and all migraine ($h^2 = 0.56$, 95% CI: 0.26–0.86), which all decreased (albeit non-significantly) after adjustment for symptoms of depression or use of antidepressant medication (Stam et al., 2010). Interestingly, a comparison of the heritability scores for depression between patients with migraine and controls found evidence for shared genetic factors only between MA and depression. Lastly, a significant correlation in genetic risk across migraine and major depressive disorder (MDD) was revealed by a recent genetic risk score (GRS) analysis (Ligthart et al., 2014).

Although providing consistent evidence for shared genetic components between migraine and depression, the twin and family studies performed to date utilized a wide variety of approaches and diagnostic measures that complicate their interpretation and comparison. Furthermore, the shared genetic variance might be described by either the same genetic and environmental factors (i.e., the same genetic and environmental factors account for susceptibility of both migraine and depression [pleiotropy]) or their potential causation (i.e., genetic and environmental factors cause a primary disorder that results in a secondary disorder; De Moor et al., 2008). In addition, some studies (Bierut et al., 1999; Larsson et al., 1995) report a higher genetic basis for migraine and depression in females compared to males, suggesting sex may play a role in the variation of the shared genetic components.

Therefore, this study utilized a variety of diagnostic measures and performed SEM (Rijsdijk & Sham, 2002) with and without sex-limitation in a large Australian, population-based twin sample to: (1) estimate the trait-specific heritability of migraine and depression; (2) estimate the shared genetic components between migraine and depression; and (3) investigate whether the shared genetic components are due to the same genetic factors or due to one disorder causing the other.

Materials and Methods

Samples

As detailed in Supplementary Figure S1, participants were drawn from three Australian twin cohorts based at QIMR

Berghofer Medical Research Institute (Heath et al., 2001; Wright & Martin, 2004). Subjects with migraine and depression status were selected and constituted the ‘merged migraine sample’ ($N = 38,279$) and ‘merged depression sample’ ($N = 60,170$), respectively. Definitions of migraine and depression were homogenized across the cohorts. Subjects also answered questions regarding demographic characteristics (e.g., sex, date of birth, zygosity), via semi-structured telephone interview and/or questionnaire. After combining the two merged samples and removal of non-twins and twins with missing status of either migraine or depression, a total of 5,319 twin pairs (2,456 MZ and 2,863 DZ pairs) remained for analysis.

Assessment of Migraine

Migraine symptom information ranged from single answer self-report (yes or no) of migraine, the ID Migraine™ Screener (Lipton et al., 2003) — three questions shown to accurately identify 93% of people with migraines, to detailed IHS diagnostic criteria (the International Classification of Headache Disorders, ICHD-3; Headache Classification Committee of the International Headache, 2013). For the collection of detailed ICHD-3 diagnostic criteria (see Table S1), participants answering ‘yes’ to ever having ‘migraine or recurrent attacks of headache’ (screening positive), then answered a number of questions relating to their symptoms. Diagnoses were determined for the two major varieties of migraine: 1.1 MO and 1.2 MA (primarily comprising 1.2.1 *Typical aura with migraine headache*), which account for 90–95% of all IHS migraines (Launer et al., 1999).

After careful merging of all available migraine information, lifetime diagnoses for migraine were made subject to data availability, according to (1) self-reported migraine, (2) the ID Migraine™ Screener, or (3) IHS ICHD-3 MO/MA diagnostic criteria. Hence, migraine status was measured in four categories according to these three criteria: non-migraine, self-report migraine (i.e., participants with positive status of self-reported measurement but negative or unknown status of the other two criteria), ID migraine (i.e., participants with positive status ID migraine™ Screener criteria but negative or unknown IHS-based migraine status), and IHS MO/MA (i.e., participants with positive status of IHS-based migraine). The ‘broad’ migraine status (i.e., any migraine) was defined when participants had reported at least one positive migraine status; and the ‘narrow’ migraine status was restricted to the clinically accepted diagnosis of IHS MO/MA.

Assessment of Depression

Participants were first asked two screening questions ‘Has there ever been two weeks or more when you were depressed or down most of the day, nearly every day?’ and ‘Has there ever been two weeks or more when you were a lot less interested in most things or unable to enjoy the things you

used to enjoy, most of the day, nearly every day?’ With at least one positive response, participants then answered additional questions (see Table S1). Lifetime depression was diagnosed according to the fourth and revised edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV-R; APA, 1994) criteria: during a 2-week period, participants who had positive responses for more than five symptoms were diagnosed as suffering MDD and participants who had 2–4 positive responses were diagnosed as suffering minor depressive disorder (MiDD). Therefore, in our study, depression status was measured in three categories: non-depressed, MiDD, and MDD. Participants with either MiDD or MDD were defined to have the ‘broad’ depression status (i.e., any depression), and the MDD status was used as the narrow, clinically accepted diagnostic measure of depression.

Statistical Analysis

All the analyses were performed in RStudio (RStudio Team, 2014). The concordance of migraine and depression for MZ and DZ twins were calculated by polychoric correlation — a measurement quantifying association between two ordinal variables that have an underlying bivariate normal distribution. Polychoric correlations were estimated using the R package *polycor* (<https://cran.r-project.org/web/packages/polycor/index.html>). The polychoric correlation assumes that underlying the observed polychotomous distribution of affection status there exists a continuous, normally distributed latent (non-observable) liability. That is, the polychoric correlation is an estimate of the correlation between two latent variables, where each latent variable is assumed to have a bivariate normal distribution. A χ^2 goodness-of-fit test is used to test whether the multiple threshold model provides a good fit to the observed data (i.e., compares the observed frequencies to those predicted by the model).

A classical twin study was used to estimate the genetic and environmental contributions to the susceptibility of a target trait. The proportion of the phenotypic variance due to genetic differences is termed the heritability (Almasy & Blangero, 2010). The model assumes the total phenotypic variance is comprised of the variances from additive genetic factors (A), non-additive (dominance) genetic factors (D), non-unique (shared) environmental factors (C), and unique environmental factors (E). MZ twins share 100% of their A, D, and C, while DZ twins share 50% of A, 25% of D, and 100% of C on average (Boomsma et al., 2002). According to these principles, the proportions of genetic and environmental contributions can be estimated by comparing concordance between MZ and DZ twins using SEM (Rijsdijk & Sham, 2002). Using the R package *OpenMx* (Boker et al., 2011), twin models were initially generated for the broad definitions of migraine and depression, and subsequent models utilized more specific and narrow definitions by excluding individuals from the analysis.

Univariate analyses were first used to examine model fit and characteristics, and estimate trait-specific variance components for migraine and depression. The liability threshold model, adjusted by age and sex, was applied to each trait. Specifically, when analyzing broad migraine and broad depression, univariate models were built independently as a comparison: the first (one-threshold) model was built using one threshold to separate two phenotype categories: non-migraine and broad migraine; and non-depressed and broad depression. The second (two-threshold) model was built using two thresholds to separate three phenotype categories: non-migraine, self-report/ID migraine, and IHS MO/MA; and non-depressed, MiDD, and MDD. When analyzing IHS MO/MA, and MDD, one threshold was utilized to separate two phenotype categories for migraine (i.e., non-migraine and IHS MO/MA) and depression (i.e., non-depressed and MDD). Starting with the full model (ACE/ADE), the reduced models (AE, CE) were then built by systematic removal of latent variables from the model. We selected the best-fitting model using the likelihood-ratio test and comparing the Akaike’s information criterion (AIC) values.

The univariate model can then be extended to the bivariate Cholesky model (Science Meanderthal, 2012), to estimate the shared genetic variance components between two traits by calculating their genetic correlation and bivariate heritability. The genetic correlation (r_G) between two traits is defined as $r_G = h_{1 \times 2}^2 / \sqrt{h_1^2 h_2^2}$, where $h_{1 \times 2}^2$ represents the genetic covariance between two traits, and h_1^2 and h_2^2 are the heritability of trait 1 and trait 2. The bivariate heritability (h^2) stands for the proportion of genetic overlap between the heritability of trait 1 and trait 2. The bivariate Cholesky models were built referring to the best-fitting models of univariate analyses for migraine and depression. By comparing results from analysis of broad migraine and depression to results using more narrow diagnoses, we can examine the influence of using different diagnostic measures on the univariate and bivariate estimates of genetic and environmental variance components.

In addition, sex-limitation models (Neale et al., 2006) for both univariate and bivariate analyses were constructed to explore the potential influence of sex-specific effects on the genetic liability to migraine and depression. A general non-scalar sex-limitation model was firstly built, including latent variables for females (i.e., A_f , C_f , and E_f) and males (i.e., A_m , C_m , and E_m) and an specific additive genetic component for males that does not correlate with the female component (i.e., A_m^S). The reduced non-scalar sex-limitation model was then constructed by removing the additional specific additive genetic variable. A restricted scalar effects sex-limitation model was also built, which assumes that all the latent variables for males are linked with the latent variables for females by a scalar effect k (i.e., $A_f = kA_m$, $C_f = kC_m$, $E_f = kE_m$). The best-fitting model was selected by the likelihood ratio test and comparing the AIC values.

Following the bivariate analyses, two approaches were used to test whether potential causation or the same genetic factors between migraine and depression best explain the shared genetic components between the two traits (De Moor et al., 2008). First, under the hypothesis of causation, one disorder would increase risk for the other via both genetic and environmental factors. Hence, both the genetic and environmental correlations between two conditions should be significant; otherwise, the hypothesis of causation is invalid. A second approach focuses on checking the presence of causal environmental factors. Briefly, in MZ twins the intrapair differences in trait 1 should be associated with intrapair differences in trait 2. The absence of this association between the intrapair differences in trait 1 and trait 2 falsifies the hypothesis of direct causation (i.e., one trait causing the other), whereas the presence of this association would support the causal hypothesis because it excludes confounding by genetic factors (i.e., the twins are genetically identical). Using this ‘MZ twin intrapair differences’ model, we computed the differences of migraine status of an MZ twin and his or her co-twin. For example, non-migraine, self-report/ID migraine and IHS MO/MA were coded as 0, 1, and 1; and non-depressed, MiDD, and MDD were coded as 0, 1, and 1, respectively. For each MZ twin pair, the intrapair difference was then calculated as either -1, 0, or 1 for broad migraine and -1, 0, or 1 for broad depression. The intrapair differences for migraine were then regressed on the intrapair differences for depression. Significant regression coefficients would be compatible with the causal hypothesis, whereas non-significant regression analysis would falsify this hypothesis.

Results

Demographics and Twin Concordance of Migraine and Depression

The mean age of 10,638 individuals was 36 ± 11 years when they participated in the survey, with a range from 18 to 89 years (Table S2). Age was used as a covariate in model fitting. The lifetime prevalence was evaluated at 45% for broad migraine (53% of females, 33% of males) and 42% for broad depression (45% of females, 37% of males), respectively; 14% of participants (18% of females, 8% of males) were diagnosed suffering IHS MO/MA and 34% of participants (38% of females, 29% of males) were diagnosed as MDD.

The polychoric correlations for MZ twins were always higher than DZ twins for the broad diagnoses of migraine and depression (Table 1), suggesting genetic contributions to both disorders. Importantly, none of the multiple-threshold model goodness-of-fit tests (one for each zygosity group) were significant at the 5% level. Therefore, these results support the validity of the multiple threshold model for the migraine and depression classifications, and indicate that they can both be conceptual-

ized as different levels of severity on a single dimension of liability. The polychoric correlations estimated for the three-category migraine and depression classifications (i.e., non-migraine, self-report/ID migraine, and IHS MO/MA; and non-depressed, MiDD, and MDD) were higher than those estimated for the two-category classifications (i.e., non-migraine and broad migraine; and non-depressed and broad depression), indicating the three-category classifications better capture the familial aggregation of the two disorders. Similar to the analysis of broad diagnoses, the estimated correlations for the more narrow clinically accepted diagnoses of IHS MO/MA and MDD were higher within MZ than DZ twins. Furthermore, the increased difference between MZ and DZ correlations indicates a stronger genetic influence to IHS MO/MA and MDD.

Results From Broad Diagnoses Analyses

Univariate analyses. Four SEMs (ACE, AE, CE, and ADE) were built to examine the genetic architecture of broad migraine and depression, based on either the one-threshold (two-category classification) model, or two-threshold (three-category classification) model. No differences in threshold liability distributions were observed within twin pairs and across zygosity groups for migraine and depression. Constraining the threshold distributions to be equal in males and females resulted in a significant deterioration in fit for migraine (p value = 5.16×10^{-61} for the one-threshold model; p value = 1.58×10^{-68} for the two-threshold model) and depression (p value = 7.64×10^{-11} for the one-threshold model; p value = 8.82×10^{-14} for the two-threshold model) when compared to a model of separate sex thresholds. We also observed that the sex differences in threshold distributions could be accounted for by a single set of liability thresholds for males plus a displacement to account for the observed higher prevalence in females for migraine and depression.

For both migraine and depression, the AE model provided a more plausible and parsimonious fit than other models (Table S3). In line with the polychoric correlation results, the two-threshold model consistently produced higher heritability estimates for migraine and depression compared to the one-threshold model. We therefore concentrated on results from the two-threshold model. For the two-threshold AE model (Table 2), the univariate heritability was estimated at 56% (95% CI: 53–60%) for migraine and 42% (95% CI: 37–46%) for depression. The non-scalar sex-limitation model without specific additive genetic effects for males provided the best fit to the data. Females had a higher heritability estimate for migraine and depression compared to males; however, the sex difference did not reach statistical significance at the 5% level, and the male–female genetic correlation was estimated at 0.92 (95% CI: 0.64–1.0) for migraine and 0.60 (95% CI: 0.20–1.0) for depression.

TABLE 1
Polychoric Correlations for Migraine and Depression According to Twin Zygosity

Two category broad classification ^a						
Broad migraine						
Zygosity (N)	MZFF (1,623)	MZMM (833)	DZFF (1,064)	DZMM (589)	DZFM (1,210)	
$\rho_{\text{polychoric}}$ (SD)	0.45 (0.03)	0.43 (0.05)	0.31 (0.05)	0.25 (0.07)	0.12 (0.05)	
95% CI	[0.39–0.52]	[0.33–0.53]	[0.23–0.40]	[0.12–0.38]	[0.03–0.21]	
Broad depression						
Zygosity (N)	MZFF (1,623)	MZMM (833)	DZFF (1,064)	DZMM (589)	DZFM (1,210)	
$\rho_{\text{polychoric}}$ (SD)	0.43 (0.03)	0.37 (0.05)	0.10 (0.05)	0.34 (0.06)	0.13 (0.05)	
95% CI	[0.37–0.50]	[0.27–0.47]	[3 × 10 ⁻³ –0.19]	[0.22–0.46]	[0.04–0.21]	
Three category broad classification ^b						
Broad migraine						
Zygosity (N)	MZFF (1,623)	MZMM (833)	DZFF (1,064)	DZMM (589)	DZFM (1,210)	
$\rho_{\text{polychoric}}$ (SD)	0.52 (0.02)	0.42 (0.04)	0.36 (0.03)	0.30 (0.06)	0.28 (0.04)	
95% CI	[0.47–0.57]	[0.33–0.51]	[0.30–0.43]	[0.19–0.41]	[0.21–0.36]	
Broad depression						
Zygosity (N)	MZFF (1,623)	MZMM (833)	DZFF (1,064)	DZMM (589)	DZFM (1,210)	
$\rho_{\text{polychoric}}$ (SD)	0.46 (0.03)	0.37 (0.05)	0.12 (0.04)	0.29 (0.06)	0.13 (0.04)	
95% CI	[0.40–0.52]	[0.28–0.47]	[0.04–0.21]	[0.17–0.40]	[0.05–0.22]	
Two category narrow classification ^c						
IHS MO/MA						
Zygosity (N)	MZFF (722)	MZMM (498)	DZFF (583)	DZMM (348)	DZFM (642)	
$\rho_{\text{polychoric}}$ (SD)	0.84 (0.03)	0.69 (0.08)	0.48 (0.06)	0.50 (0.11)	0.60 (0.06)	
95% CI	[0.79–0.89]	[0.54–0.84]	[0.36–0.59]	[0.29–0.71]	[0.49–0.71]	
MDD						
Zygosity (N)	MZFF (1,401)	MZMM (695)	DZFF (902)	DZMM (512)	DZFM (1,024)	
$\rho_{\text{polychoric}}$ (SD)	0.53 (0.03)	0.45 (0.06)	0.15 (0.05)	0.30 (0.07)	0.16 (0.05)	
95% CI	[0.47–0.60]	[0.34–0.55]	[0.05–0.25]	[0.16–0.44]	[0.06–0.26]	

Note: $\rho_{\text{polychoric}}$ = polychoric correlation; 95% CI: 95% confidence interval; SD = standard deviation; MZFF = female MZ twins; MZMM = male MZ twins; DZFF = female DZ twins; DZMM = male DZ twins; DZFM = opposite-sex DZ twins; N = number of twin pairs.

^aTwo phenotype categories for broad migraine: non-migraine and self-report/ID migraine/IHS MO/MA; two phenotype categories for broad depression: non-depressed and MiDD/MDD.

^bThree phenotype categories for broad migraine: non-migraine, self-report/ID migraine and IHS MO/MA; three phenotype categories for broad depression: non-depressed, MiDD and MDD. $\rho_{\text{polychoric}}$ (SD).

^cTwo phenotype categories for narrow migraine: non-migraine and IHS MO/MA; two phenotype categories for narrow depression: non-depressed and MDD.

TABLE 2
Univariate Analyses for Broad Migraine and Broad Depression With And Without Sex-Limitation Based on Two-Threshold Model

Disorders	Sex-limitation					
	Total sample		Female		Male	
	A	E	A	E	A	E
Broad migraine ^a	0.57 (0.53–0.60)	0.44 (0.40–0.47)	0.60 (0.55–0.64)	0.40 (0.36–0.45)	0.49 (0.40–0.55)	0.52 (0.45–0.60)
Broad depression ^a	0.42 (0.37–0.46)	0.58 (0.54–0.63)	0.44 (0.38–0.50)	0.56 (0.50–0.62)	0.40 (0.32–0.48)	0.60 (0.52–0.68)

Note: A = additive genetic factors; E = unique environmental factors.

^aThree phenotype categories for broad migraine: non-migraine, self-report/ID migraine, and IHS MO/MA; three phenotype categories for broad depression: non-depressed, MiDD, and MDD.

Bivariate analyses. Bivariate Cholesky SEMs were utilized to estimate variance components shared between migraine and depression. As for the univariate SEM analyses, the two-threshold AE/AE model best fit the data. The trait-specific heritability of broad migraine (56%) and depression (42%) were essentially the same as the estimates from the univariate analyses (Tables 2 and 3). Importantly, a significant additive genetic correlation ($r_G = 0.36$, 95% CI: 0.29–0.43) and bivariate heritability ($h^2 = 5.5\%$, 95% CI: 3.6–7.8%) was observed between migraine and depression. The unique environmental correlation was not significant ($r_E = 0.05$, 95% CI: -0.01–0.11) and the bivariate unique

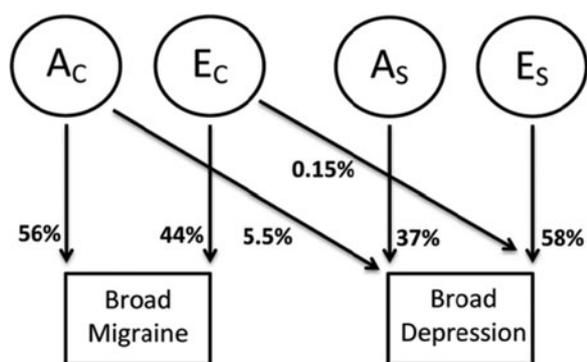
environmental variance was very small ($V_E = 0.15\%$, 95% CI: 0.00034–0.72%). Under the sex-limitation model, no significant difference in r_G and h^2 was observed between females and males.

A path diagram portraying this best-fitting Cholesky model is displayed in Figure 1. The principal genetic features of the model are explained as follows. First, the common additive genetic factors accounting for 56% (95% CI: 53–60%) of the variance in migraine also account for 5.5% (95% CI: 3.6–7.8%) of the variance in depression. Second, specific additive genetic factors account for 37% (95% CI: 32–41%) of the variance in broad depression. Individual

TABLE 3**Bivariate Analyses for Broad Migraine and Broad Depression With and Without Sex-Limitation Based on Two-Threshold Model**

Disorders	Total sample		Sex-limitation			
	A	E	Female		Male	
Broad migraine ^a	0.56 (0.53–0.60)	0.44 (0.40–0.47)	0.60 (0.55–0.64)	0.40 (0.36–0.45)	0.49 (0.41–0.56)	0.51 (0.44–0.59)
Broad depression ^a	0.42 (0.37–0.47)	0.58 (0.53–0.63)	0.44 (0.38–0.50)	0.56 (0.50–0.62)	0.40 (0.31–0.48)	0.60 (0.52–0.69)
Bivariate variance	0.055 (0.036–0.078)	1.5×10^{-3} (3.4×10^{-6} – 7.1×10^{-3})	0.047 (0.026–0.074)	4.1×10^{-6} (4.1×10^{-6} – 4.2×10^{-6})	0.058 (0.024–0.11)	7.3×10^{-3} (2.1×10^{-5} –0.028)
Correlation	0.36 (0.29–0.43)	0.050 (-0.011–0.11)	0.32 (0.25–0.41)	2.7×10^{-3} (-0.075–0.080)	0.38 (0.25–0.52)	0.11 (5.4×10^{-3} –0.21)

Note: A = additive genetic factors; E = unique environmental factors.

^aThree phenotype categories for broad migraine: non-migraine, self-report/ID migraine, and IHS MO/MA; three phenotype categories for broad depression: non-depressed, MiDD, and MDD.**FIGURE 1**

Path diagrams of the bivariate Cholesky models for broad diagnoses. The square frame represents the observed trait and the circle frame represents the latent variable. A_C and E_C stand for the additive genetic variable and unique environmental variable common to migraine and depression; A_S and E_S stand for the additive genetic variable and unique environmental variable specific to depression.

(non-shared) environmental factors explain the remaining variance in liability to migraine and depression.

Results From Narrow Diagnoses Analyses

Univariate analyses. To improve the sensitivity of true positive cases and specificity of true negative controls for migraine and depression, we next performed SEM analyses for the more narrow, clinically accepted diagnoses of IHS MO/MA and MDD. As for the broad diagnoses, no differences in threshold liability distributions were observed within twin pairs and across zygosity groups for IHS MO/MA and MDD and single set of liability thresholds could be utilized for males with a displacement to account for the observed higher prevalence in females. The heritability of IHS MO/MA was estimated after excluding individuals with the broader ID migraine and self-report definitions, by selecting only individuals who provided responses to the ICHD-3 based questionnaire for MO/MA.

Although the number of twins analyzed reduced from 5,319 to 2,793 (Table 4), the best-fitting ACE model data (see Table S4) estimated a heritability of 59% (95% CI: 43–76%) for IHS MO/MA. Similarly, the heritability of MDD was calculated based on the subset of individuals who were diagnosed with non-depressed or MDD (i.e., removing the cases of MiDD; sample size decreased from 5,319 to 4,534 twin pairs). For the best-fitting AE model (Table S4), the heritability was estimated at 49% (43–54%) for MDD. For both IHS MO/MA and MDD, the non-scalar sex-limitation model after removing the specific additive genetic variable for males provided the best fit to our data, with an estimated male–female genetic correlation of 1 (95% CI: 0.31–1.0) for IHS migraine and 0.64 (95% CI: 0.23–1.0) for MDD. Although heritability estimates were slightly higher in females compared to males, sex-limitation models indicated no significant heritability differences between females and males.

Bivariate analyses. The variance components shared between IHS MO/MA and MDD were next estimated using one-threshold bivariate Cholesky SEMs. As for the univariate SEMs, the ACE/AE bivariate Cholesky model provided the best overall fit for the combined IHS MO/MA and MDD sample ($N = 2,406$, see Table S5, section 3). Similar to the univariate results, the trait-specific heritabilities from the bivariate model were increased relative to the broad diagnoses, being estimated at 53% (95% CI: 35–72%) for IHS MO/MA and 52% (95% CI: 44–59%) for MDD (Table 5). Importantly, we observed a substantially increased additive genetic correlation ($r_G = 0.51$, 95% CI: 0.37–0.69) and bivariate heritability ($h^2 = 13.3\%$, 95% CI: 7.0–14.5%) between IHS MO/MA and MDD, compared to the results of broad migraine and depression. Sex-limitation models indicated no significant difference in r_G and h^2 between females and males.

The best-fitting bivariate Cholesky model for IHS MO/MA and MDD is portrayed in the path diagram illustrated in Figure 2. The principal genetic features of this

TABLE 4
Univariate Analyses for IHS MO/MA and MDD with and Without Sex-Limitation

Disorders	Total sample			Sex-limitation					
				Female			Male		
	A	C	E	A	C	E	A	C	E
IHS MO/MA	0.59 (0.43–0.76)	0.25 (0.090–0.39)	0.16 (0.12–0.21)	0.65 (0.46–0.82)	0.19 (0.044–0.36)	0.16 (0.11–0.22)	0.43 (0.083–0.75)	0.32 (0.051–0.62)	0.25 (0.15–0.39)
MDD	0.49 (0.43–0.54)	-	0.51 (0.46–0.57)	0.51 (0.44–0.57)	-	0.49 (0.43–0.56)	0.46 (0.36–0.56)	-	0.54 (0.44–0.64)

Note: A = additive genetic factors; C = non-unique environmental factors; E = unique environmental factors.

TABLE 5
Bivariate Analyses for IHS MO/MA and MDD With and Without Sex-Limitation

Disorders	Total sample			Sex-limitation					
				Female			Male		
	A	C	E	A	C	E	A	C	E
IHS MO/MA	0.53 (0.35–0.72)	0.29 (0.13–0.44)	0.18 (0.13–0.24)	0.60 (0.39–0.80)	0.23 (0.054–0.41)	0.16 (0.11–0.23)	0.32 (0.040–0.70)	0.36 (0.056–0.62)	0.32 (0.19–0.48)
MDD	0.52 (0.44–0.59)	-	0.48 (0.41–0.56)	0.56 (0.46–0.65)	-	0.44 (0.35–0.50)	0.42 (0.27–0.56)	-	0.58 (0.44–0.73)
Bivariate variance	0.13 (0.070–0.25)	-	2.0 × 10 ⁻⁴ (8.6 × 10 ⁻¹¹ –0.018)	0.094 (0.038–0.20)	-	0.016 (5.7 × 10 ⁻⁷ –0.074)	0.13 (0.020–0.52)	-	0.047 (1.6 × 10 ⁻⁶ –0.18)
Correlation	0.51 (0.37–0.69)	-	-0.020 (-0.19–0.15)	0.41 (0.26–0.60)	-	-0.19 (-0.41–0.036)	0.56 (0.19–1)	-	0.29 (-8.5 × 10 ⁻⁴ –0.56)

Note: A = additive genetic factors; C = non-unique environmental factors; E = unique environmental factors.

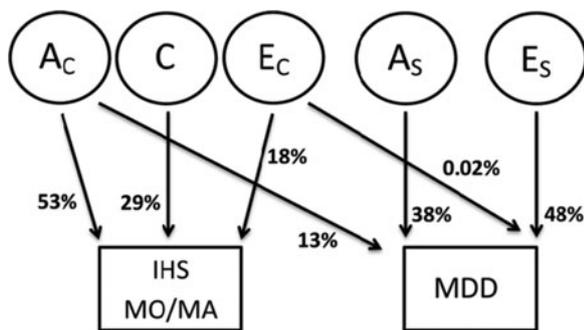


FIGURE 2
Path diagrams of the bivariate Cholesky models for narrow diagnoses. The square frame represents the observed trait and the circle frame represents the latent variable. A_C and E_C stand for the additive genetic variable and unique environmental variable common to IHS MO/MA and MDD; A_S and E_S stand for the additive genetic variable and unique environmental variable specific to MDD. C stands for the non-unique environmental variable specific to IHS MO/MA.

model are as follows. First, the common additive genetic factors accounting for 53% (95% CI: 35–72%) of the variance in IHS MO/MA also account for 13% (95% CI: 7–24%) of the variance in MDD. Second, there are specific additive genetic factors accounting for 38% (95% CI: 26–48%) of the variance in MDD. Individual (non-shared) environmental factors explain the remaining variance in liability to IHS MO/MA and MDD.

Shared Etiology or Direct Causation?

For both broad and narrow diagnoses, we found that the comorbidity between migraine and depression is best explained by a shared etiology (including shared genetic factors) rather than a causal relationship. That is, the bivariate analyses found a significant genetic correlation and non-significant environmental correlation between migraine and depression. Furthermore, there was no significant association between the MZ intrapair differences for migraine and depression (*p* value = .67 for the two-category broad migraine/depression status; *p* value = .66 for the three-category broad migraine/depression status; and *p* value = .73 for IHS MO/MA and MDD).

Discussion

This is the largest twin study to date on evaluating the genetic architecture of migraine and depression as well as their potential shared genetic components. Several findings are worth noting.

First, the heritability of broad migraine and depression was estimated at 56% and 42%, respectively, consistent with previous European population-based studies (Bierut et al., 1999; Duncan et al., 2014; Honkasalo et al., 1995; Mulder et al., 2003; Nes et al., 2013; Svensson et al., 2003). This consistency extends to our finding of no significant non-additive genetic (D) and non-unique environmental (C) components. Also, in line with previous findings (Nyholt

et al., 2004), our results support the multiple threshold model, and indicate that different migraine classifications (self-report, ID migraine, and IHS MO/MA) can be conceptualized as different levels of severity on a single dimension of liability. Analogously, MiDD and MDD exist as different severity levels on a single dimension of liability. These findings are nicely reflected by the three-category (two-threshold) model capturing more of the genetic contribution to both migraine and depression compared to the two-category (one-threshold) model. Therefore, broadening the migraine and depression phenotype in genetic studies by including individuals with sub-IHS diagnoses, such as self-reported and ID migraine and sub-MDD diagnoses such as MiDD, should facilitate the identification of genetic risk factors due to improved power via increased sample size. That said, for the two-category definitions, the enhanced diagnostic sensitivity and specificity of narrow IHS MO/MA and MDD produced higher heritability estimates compared to the results from the one-threshold broad migraine and depression analyses, with heritability increasing from 48% to 59% for IHS MO/MA and from 40% to 49% for MDD, respectively. These latter results suggest that it might be important to model different diagnostic categories (e.g., via multinomial or ordinal logit models) to maximize power in genetic association studies.

Second, and also in line with three previous twin- and family-based studies (Ligthart et al., 2010; Schur et al., 2009; Stam et al., 2010), both additive genetic correlation and bivariate heritability between broad migraine and depression ($r_G = 0.36$, 95% CI: 0.29–0.43; $h^2 = 5.5\%$, 95% CI: 3.6–7.8%) were significantly detected, indicating the presence of shared genetic components between the two disorders. Not surprisingly, both r_G and h^2 substantially increased between IHS MO/MA and MDD ($r_G = 0.51$, 95% CI: 0.37–0.69; $h^2 = 13.3\%$, 95% CI: 7.0–24.5%). It is also worth noting that r_G and h^2 increase (see Table S5, section 4) between broad migraine and MDD ($N = 4,534$, $r_G = 0.39$, 95% CI: 0.30–0.47; $h^2 = 7.3\%$, 95% CI: 4.5–10.9%) and between IHS MO/MA and broad depression ($N = 2,793$, $r_G = 0.46$, 95% CI: 0.33–0.62; $h^2 = 9.7\%$, 95% CI: 5.0–17.4%). These findings indicate that the shared genetic components between the two disorders can also be conceptualized on a single dimension of liability and exist regardless of the specific migraine and depression definition studies. Our finding of a slightly smaller bivariate heritability compared with the previous study of (Schur et al., 2009) is most likely due to differences in sample characteristics (e.g., the previous study only used female twins) and the diagnostic approaches and definitions of migraine and depression.

Third, our results indicate that the co-occurrence of migraine and depression is most likely due to a shared etiology comprising shared genetic factors that influence both disorders rather than one primary disorder causing the other secondary disorder. Contrastingly, a Dutch twin study by Ligthart et al. (2010) suggested a causal bidirectional

relationship between migraine and anxious depression. This study reported a significant environmental correlation between MZ intrapair differences for LCA-derived migraine and anxious depression using only MZ twin pairs discordant for both disorders. However, when only utilizing discordant MZ twin pairs in our study, the correlation between MZ intrapair differences for both broad and narrow migraine and depression was still non-significant (p value = .93 for the two-category broad migraine/depression status; p value = .51 for the three-category broad migraine/depression status; and p value = .19 for IHS MO/MA and MDD). Comparison with the current findings is complicated due to the use of different diagnostic measures. First, the Dutch twin study coded migraine status by utilizing an empirically derived migrainous headache classification based on LCA clustering of reported IHS MO/MA symptoms, and the survey questionnaire did not include the questions corresponding to the MO-related symptom ‘unilateral location’ and MA-related aura characteristic symptoms, compared to the questionnaire used in our study (see Table S1). Additionally, the Dutch study analyzed the role of anxious depression, which consisted of a factor score based on several measures of anxiety, depression, and neuroticism. Further research will be required to determine whether anxiety and/or neuroticism play a confounding role in co-occurrence of migraine and depression.

Our study also has some limitations. First, both migraine and depression status were diagnosed using self-reported questionnaire data, as opposed to the gold-standard of clinical-based interviews by neurologists or psychologists. Although our approach may result in some misclassification of migraine and depression status, it is not feasible to perform clinic-based interviews in samples larger enough to provide sufficient power for such familial aggregation studies. Moreover, our approach enabled narrow diagnoses of migraine and depression that satisfy clinically accepted criteria. Furthermore, our estimated lifetime prevalence of IHS MO/MA and DSM-III-R-based MDD are in a good agreement with published estimates (Arroyo-Quiroz et al., 2014; Bierut et al., 1999; Buse et al., 2012; Kendler et al., 1992). In addition to the clinically accepted definitions of IHS MO/MA and DSM MDD, our study utilized other diagnostic measurements or criteria of migraine (i.e., self-report migraine and ID migraine) and depression (i.e., MiDD) to both increase study power and examine the influence of different phenotypic distributions on genetic modeling of migraine and depression. Lastly, although this study did not analyze MO and MA separately, considering MO is the most common IHS MO/MA subtype and our results supporting the multiple threshold model and single liability of dimension, our findings do not corroborate the previous observation of genetic overlap between depression and MA and not MO (Stam et al., 2010).

Several conclusions can be drawn from our study. First, genetic factors contribute significantly to the susceptibility

to both migraine and depression, with no significant gender differences in the magnitude (sex-limitation) and no sex-specific effects (i.e., effects expressed in one sex but not the other) on risk for migraine and depression. Second, both univariate and bivariate heritability of migraine and depression increase with increased severity of the two disorders. Lastly, our results indicate that for both broad and narrow definitions, the observed comorbidity between migraine and depression can be explained by a shared etiology (rather than a causal relationship) that almost entirely comprises shared underlying genetically determined disease mechanisms. The identification of shared underlying genetic factors will improve our understanding of the relationship between migraine and co-occurring depression and facilitate the detection of novel pathways and thus identify new targets for drug therapy.

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Supplementary Material

To view supplementary material for this article, please visit <http://dx.doi.org/10.1017/thg.2016.46>

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