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Migraine symptomatology and major depressive disorder

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Abstract

Introduction and objective: Migraine and major depressive disorder (MDD) frequently co-occur, but it is unclear whether depression is associated with a specific subtype of migraine. The objective of this study was to investigate whether migraine is qualitatively different in MDD patients ($N = 1816$) and non-depressed controls ($N = 3428$).

Methods: Migraine symptom data were analyzed using multi-group Latent Class Analysis, and a qualitative comparison was made between the symptom profiles of MDD patients and controls, while allowing for differences in migraine prevalence and severity between groups.

Results: In both groups, three migrainous headache classes were identified, which differed primarily in terms of severity. Both mild and severe migrainous headaches were two to three times more prevalent in MDD patients. Migraine symptom profiles showed only minor qualitative differences in the MDD and non-MDD groups: in the severe migrainous headache class, significant differences were observed only in the prevalence of *aggravation by physical activity* (83% and 91% for the non-MDD and MDD groups, respectively) and *aura* (42% vs. 53%, respectively).

Conclusion: The similar overall symptom profiles observed in the MDD and non-MDD subjects suggest that a similar disease process may underlie migraine in both groups.

Keywords

Migraine, major depressive disorder, comorbidity, epidemiology

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Introduction

A vast amount of literature describes the comorbidity of migraine and major depressive disorder (MDD). Comorbidity studies of depression and the two most common types of migraine—migraine with aura (MA) and migraine without aura (MO), consistently report a higher prevalence of migraine among depressed individuals compared to the general population (1–4). There is currently no verified explanation for this comorbidity, although it has been suggested that common biological pathways, such as the serotonergic and dopaminergic system, may be involved (5,6). An important question that needs to be answered is whether depression is associated with a specific subtype or form of migraine. Several studies report that MA is more strongly correlated with depression than MO (1,7–9). One interpretation of this finding is that migraine patients with comorbid depression suffer from a different type of migraine than 'pure' migraineurs, which causes them to experience more aura symptoms. Alternatively, however, this finding might indicate that individuals with more severe forms of migraine have a higher risk of developing depression. Given the symptomatic overlap between MO and MA, and the lack of evidence that these two disorders are etiologically distinct subtypes of migraine (10,11) the second interpretation seems to be a plausible explanation.

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To investigate whether depression is associated with a specific type of migraine, we reverse the question: are the migraines of depressed and non-depressed individuals similar in characteristics? If there are observable qualitative differences in the manifestation of migraine in depressed and non-depressed individuals, this may indicate there is a difference in the etiology of migraine in both groups. To address this issue, we compared migraine symptomatology in a large sample of MDD patients and in a control sample, selected for low risk of depression. Using latent class analysis (LCA), individuals were empirically classified according to the pattern of headache symptoms they reported. Then the headache symptom profiles were compared between the MDD and the non-MDD groups. Thus, qualitative differences in migraine symptomatology could be assessed while still allowing for anticipated differences in prevalence and severity.

Methods

Sample

The depressed sample in this study consisted of MDD cases diagnosed according to DSM-IV criteria (12) with the Composite International Diagnostic Interview [CIDI] (13). The majority of MDD cases were originally recruited for the Netherlands Study of Depression and Anxiety [NESDA] (14). Of the 2981 NESDA participants, 2601 filled in a self-report questionnaire that provided information on migraine. Of these individuals, 1636 were diagnosed with lifetime MDD (1017 of whom had a diagnosis of MDD in the past year). All individuals with a lifetime diagnosis of MDD were included in this study. Seven hundred fifty-six were recruited through primary care, 561 through specialized mental health care and another 319 from the general population. Individuals who did not have a lifetime MDD diagnosis were not included. All NESDA participants underwent a four-hour baseline assessment at one of seven clinic sites between September 2004 and February 2007. Part of this assessment were an interview on somatic health, functioning and health care use, and the administration of several written questionnaires (15), which included a section on migraine symptomatology (see below). A detailed description of sampling and ascertainment procedures for the NESDA study can be found elsewhere (14).

The remainder of the study sample consisted of volunteer members of the Netherlands Twin Registry (NTR), based at the department of Biological Psychology at VU University in Amsterdam. In this group, the migraine data were collected as part of a longitudinal study on health, lifestyle and personality. The data used in the present study were collected in 2002 and 2004. Data collection procedures are described in detail elsewhere (16,17). These surveys included the same headache section that was included in the NESDA questionnaire. When a participant answered the headache section in both surveys, the most recent (2004) survey was used. Headache data were available for a total of 4047 families. In a subset of these families, one or more individuals had been diagnosed with MDD in an earlier study of anxious depression (18), based on a CIDI interview. In addition, an anxious depression factor score was constructed based on data from the 2002 survey, using several measures of anxiety, depression and neuroticism (see Boomsma et al. (18) for details). The 2004 survey included the NEO Five Factor Inventory (19), which has a neuroticism subscale.

NTR participants with a diagnosis of MDD based on the CIDI interview were included as additional MDD cases. In case of multiple individuals with MDD within a family, the individual with the highest anxious depression or neuroticism score was included. With this procedure an additional 180 MDD cases were selected, resulting in a total number of 1816 individuals with MDD.

The non-depressed control sample was also selected from the NTR, after excluding the families in which one or more individuals had been diagnosed as MDD cases. One person was selected from each family to maintain a selection of unrelated controls. Within each family, individuals were ranked based on their anxious depression score. This information was available for 3209 families. In families with no anxious depression scores available ($N = 594$), the neuroticism scale of the NEO-Five Factor Inventory (NEO-FFI) was used. From each family, the individual with the lowest anxious depression or neuroticism score was selected. For a few families ($N = 4$) no information on anxious depression or neuroticism was available, in which case one individual was drawn at random. All individuals with an anxious depression or neuroticism score higher than one standard deviation (SD) above the mean were excluded. This resulted in a low-risk control sample of 3428 individuals.

The control sample included 1379 male and 2049 female participants. The MDD sample included 553 males and 1263 females. The mean age was 42.6 ($\pm$12.4) in the MDD sample and 41.1 ($\pm$14.0) in the control sample.

Migraine measures

Migraine was assessed based on the International Classification of Headache Disorders, second edition (ICHD-II), criteria of the International Headache Society (IHS) (20). Not only the endpoint diagnosis but especially its components (i.e. individual migraine symptoms/characteristics) were studied, to see whether

'symptom profiles' differed between the MDD group and the controls. The presence of these symptoms was assessed using questionnaire items which provided information on the IHS criteria for migraine. The headache section of the questionnaires was preceded by a screening question (''Do you ever experience headache attacks, for instance, migraine?''). Individuals screening positive then answered the remaining questions. The questionnaire items are described in Table 1.

The information obtained from the questionnaire items was recoded as follows: 0 = screened negative, 1 = screened positive, but negative for symptom, 2 = screened positive, and positive for symptom. This was done for the variables *>= 5 episodes*, *4–72 hours* (duration), *pulsating*, *moderate/severe* (pain intensity), *aggravation* (by physical activity), *nausea/vomiting, photo-/phonophobia* and (visual) *aura*. These symptom variables were also used to establish a diagnosis according to the official IHS criteria (see Table 1).

Statistical analyses

LCA (21,22) is a statistical method that classifies individuals based on their pattern of responses or characteristics. A latent class model describes the relationship between a set of categorical observed variables (indicators) and an unobserved categorical variable. The categories of this underlying variable are referred to as latent classes, or clusters. Within each cluster, the observed variables are assumed to be independent. In other words, the relationship between the observed variables (in this case, migraine symptoms) is explained entirely by the latent variable (in this case, 'type of headache'). The parameters in an LCA model are the prevalence of each class, and the probability, given class membership, that an individual is positive for each symptom (the conditional probabilities). They are estimated with the expectation-maximization (EM) algorithm (23). For each individual, the most likely class membership can then be calculated, based on the pattern of symptoms reported.

The aim of this study was to determine whether the same latent classes of headache sufferers could be identified in the MDD patients and the controls. We first estimated the number of latent classes present in the two samples. Then the symptom profiles of each group were compared by running a multiple-group LCA with the headache symptoms as the indicator variables. Differences in the symptom profiles were tested by equating the conditional probabilities for the classes across groups, and assessing the change in model fit by comparing log-likelihood values. Because migraine is known to be more prevalent in females than in males, it was first tested whether symptom profiles differed across sex. Next, profile differences between the MDD patients and the controls were assessed. Finally, classification results were compared between the two groups to test for differences in prevalence. All latent class analyses were performed in Mplus version 5 (Muthén & Muthén Los Angeles, CA, USA), using the ''KNOWNCLASS'' option to allow multi-group LCA. The number of random sets of starting values for the initial stage was set to 250 and in the final stage 50 maximum likelihood optimizations were specified. The number of classes was determined using the Bayes Information Criterion (BIC), with a lower BIC indicating better fit to the data.

Results

MDD patients showed a significantly higher prevalence of all migraine symptoms (Table 2). Generally,

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

IHS, International Headache Society. *In the present study, individuals were considered positive for a full IHS migraine diagnosis if they fulfilled the following criteria: A; B; at least two of C2, C3 and C4; at least one of D1 and D2.†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.

Table 2. The prevalence of migraine symptoms and IHS migraine diagnosis in the depressed and non-depressed groups

	Males						Females						All					
	MDD− (*N* = 1379)		MDD+ (*N* = 553)				MDD− (*N* = 2049)		MDD+ (*N* = 1263)				MDD− (*N* = 3428)		MDD+ (*N* = 1816)			
	N	%	*N*	%	OR	95% CI	*N*	%	*N*	%	OR	95% CI	*N*	%	*N*	%	OR	95% CI
Positive for screening question	195	14%	241	44%	4.76	(3.80–5.97)	581	29%	735	60%	3.60	(3.10–4.18)	776	23%	976	55%	4.06	(3.59–4.60)
>= 5 episodes	159	12%	226	41%	5.30	(4.19–6.72)	536	26%	710	56%	3.62	(3.12–4.21)	695	20%	936	52%	4.18	(3.69–4.74)
4–72 hours	99	7%	109	20%	3.17	(2.37–4.25)	365	18%	447	35%	2.53	(2.15–2.97)	464	14%	556	31%	2.82	(2.45–3.24)
Pulsating	102	7%	116	21%	3.32	(2.49–4.43)	345	17%	379	30%	2.12	(1.79–2.50)	447	13%	495	27%	2.50	(2.17–2.88)
Moderate/severe	158	11%	220	40%	5.11	(4.0–6.48)	556	27%	707	56%	3.41	(2.95–3.96)	714	21%	927	51%	3.96	(3.50–4.49)
Aggravation	100	7%	174	31%	5.87	(4.48–7.70)	404	20%	614	49%	3.85	(3.30–4.50)	504	15%	788	43%	4.45	(3.90–5.08)
Nausea/vomiting	52	4%	67	12%	3.52	(2.41–5.13)	285	14%	341	27%	2.29	(1.92–2.73)	337	10%	408	22%	2.66	(2.27–3.11)
Photo-/phonophobia	98	7%	146	26%	4.69	(3.55–6.20)	377	18%	550	44%	3.42	(2.92–4.01)	475	14%	696	38%	3.86	(3.37–4.42)
Aura	39	3%	92	17%	6.86	(4.65–10.12)	184	9%	306	24%	3.24	(2.66–3.95)	223	7%	398	22%	4.03	(3.39–4.81)
IHS migraine	42	3%	63	11%	4.09	(2.73–6.13)	199	10%	328	26%	3.26	(2.69–3.96)	241	7%	391	22%	3.63	(3.05–4.31)

MDD+, depressed; MDD−, non-depressed; OR, odds ratio indicating risk of each symptom/diagnosis, given depression status; CI, confidence interval; IHS, International Headache Society.

symptom prevalence was two to three times higher in the MDD group than in the control group, confirming the strong association that exists between migraine and depression at the level of individual migraine symptoms. Table 2 also shows the number of individuals who would receive a full diagnosis of migraine (either MO or MA), according to IHS criteria. The number of full IHS migraine diagnoses is significantly higher in the MDD patients (22%) than in the controls (7%). The relationship between migraine and MDD was somewhat more pronounced for males than for females; generally, migraine symptoms were three to four times more prevalent in the depressed compared to the non-depressed males. In females the risk was about two times higher for the MDD group.

Initially, an exploratory LCA was performed to determine the appropriate number of classes and to compare the symptom profiles in males and females. A two-group analysis was run with sex as the grouping (''KNOWNCLASS'') variable, thus allowing for different symptom profiles in males and females. Sex was also modeled as a covariate on class membership, to allow for different migraine prevalences in males and females. This analysis was run first on cases only, and then on controls only. Based on the BIC values, a three-class model had the best fit to the data in both the cases and the controls: in cases, the three-class model produced a BIC of 13542, compared to a BIC of 13671 for a two-class model and BIC of 13760 for a four-class model; in controls, the three-class model produced a BIC of 16112, compared to a BIC of 16209 for a two-class and BIC of 16348 for a four-class model.

Next, the conditional probabilities (i.e. the symptom profiles) were equated for males and females, assuming the three-class model (Table 3). This did not result in a significant change in model fit in either cases or controls ($\chi^2(48)=16.55$, $p=1.000$ for cases, $\chi^2(48)=38.29$, $p=.841$ for controls).

As the symptom profiles did not differ between males and females, we proceeded with a two-group model (with three classes) in which the conditional probabilities were equal for males and females but differed between the MDD and control group. Sex and case/control status were maintained in the model as covariates, because of the known differences in migraine prevalence across these groups. Figure 1 shows the symptom profiles for this model, with the symptoms on the x-axis, the conditional probabilities for each symptom on the y-axis and the error bars indicating 95% confidence intervals. Class 0 represents the group of individuals screening negative for headaches, who did not answer further questions. These individuals have conditional probabilities of 0 for all symptoms. Class 1 individuals have headaches with migrainous features, but most of these would not be diagnosed as migraine patients. The individuals in class 2 can be characterized as migrainous headache sufferers, with headaches that typically include the majority of migraine features. The most important difference between class 1 and class 2 appears to be the overall severity of the headaches. Class 1 and class 2 look similar, but all symptoms are more prevalent in class 2. The distinction between class 1 and class 2 is most pronounced for the symptoms *nausea/vomiting*, *photo-/phonophobia* and *aura*. Of the individuals in class 1, 3% satisfied the IHS criteria for migraine (all MO). In class 2, 55% met these criteria (55% MO, and 40% MA and 5% unclassified due to missing aura data).

It can be seen that the profiles of MDD and non-MDD subjects are very similar, although some subtle differences are observed in the prevalence of *aggravation*, *photo-/phonophobia* and *aura* (only the estimates for *aggravation* and *aura* showed non-overlapping confidence intervals for the MDD and control groups). These symptoms had higher conditional probabilities in the MDD patients than in the controls in both class 1 (mild symptoms) and class 2 (severe symptoms). In class 1 the differences were more pronounced (with endorsement frequencies of 45% vs. 64% for aggravation and 15% vs. 24% for aura, in non-MDD and MDD subjects, respectively) than in class 2 (83% versus 91% for aggravation and 42% versus 53% for aura). The overall significance of

Table 3. Model fit statistics and comparisons for the baseline and restricted three-class LCA models

Model	*N*	npar	LL	Scaling correction factor	Compared to	χ^2	d.f.	*p* value
1 Male vs. female; different profiles, non-depressed cohort	3428	101	−7645.22	1.014				
2 Male vs. female; equated profiles, non-depressed cohort	3428	53	−7664.55	1.018	1	38.29303	48	0.841
3 Male vs. female; different profiles, depressed cohort	1816	101	−6392.11	1.014				
4 Male vs. female; equated profiles, depressed cohort	1816	53	−6400.55	1.009	3	16.55287	48	1.000
5 Depressed vs. non-depressed; different profiles	5244	103	−14024.1	1.013				
6 Depressed vs. non-depressed; equated profiles	5244	55	−14097.8	1.013	6	145.6663	48	0.000

LCA, latent class analysis; npar, number of parameters; LL, Log-likelihood; d.f., degrees of freedom.

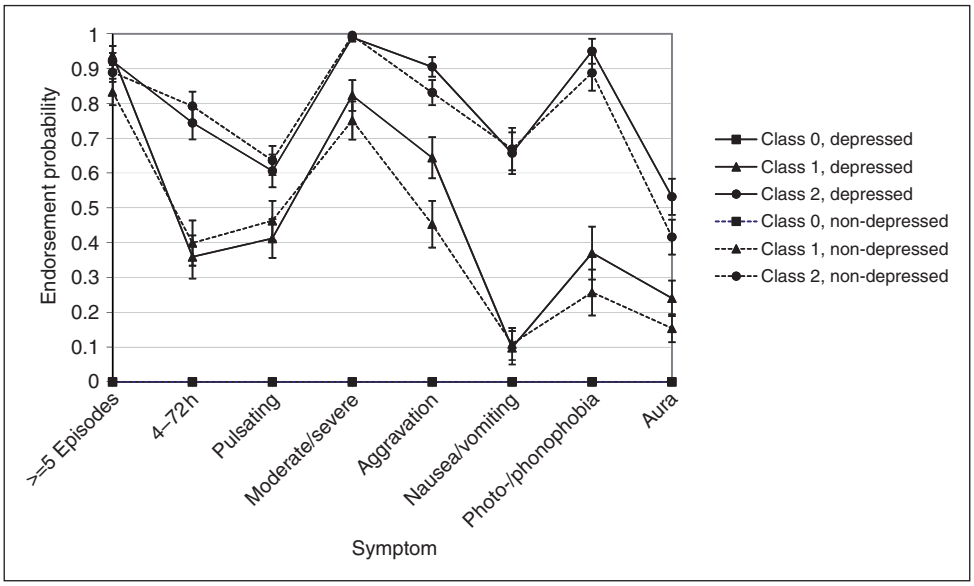

Figure 1. Symptom profiles for the two-group, three-class model, with the symptoms on the x-axis, the conditional probabilities for each symptom on the y-axis and the error bars indicating 95% confidence intervals. Class 0 represents the group of individuals screening negative for headaches, who did not answer further questions.

Table 4. Class prevalences in the four analysis groups (male/female, depressed/non-depressed), based on best-fitting model

		MDD−		MDD+	
		N	Class proportion	*N*	Class proportion
Males	Class 0	1179	85.5%	306	55.3%
	Class 1	123	8.9%	161	29.1%
	Class 2	77	5.6%	86	15.6%
	Total	1379	100.0%	553	100.0%
Females	Class 0	1415	69.1%	497	39.4%
	Class 1	204	10.0%	262	20.7%
	Class 2	430	21.0%	504	39.9%
	Total	2049	100.0%	1263	100.0%

MDD+, depressed; MDD−, non-depressed.

these profile differences was tested by equating the conditional probabilities for MDD patients and controls, which produced a significantly worse fit to the data ($\chi^2(48) = 145.67$, $p < .0001$).

Table 4 shows the classifications resulting from the best-fitting model, which assumes the same conditional probabilities for males and females but not for MDD and non-MDD individuals. In both sexes, class prevalence differed significantly across depression status ($\chi^2(2)=202.707$, $p < .0001$ in males and $\chi^2(2)=283.258$, $p < .0001$ in females). The prevalence of both class 1 and class 2 headaches was significantly higher in MDD patients than in controls.

Discussion

The aim of this study was to compare migraine symptom profiles in MDD patients and controls, empirically classified according to their pattern of headache symptoms. If similar headache classes and symptom profiles would arise empirically and independently in MDD patients and controls, this would be consistent with the hypothesis that we are observing the same disorder in the two groups. Substantial qualitative differences, however, would suggest a difference in etiology.

As expected, the prevalence of migraine was higher in MDD patients. Importantly, all migraine symptoms had an increased prevalence in the MDD group, and MDD patients were overrepresented in both the mild and severe migraine classes. This is consistent with the literature on the comorbidity of migraine and MDD. Qualitatively, however, migraine was very similar in MDD patients and controls. Similar symptom profiles were observed in the two groups, although a few differences should be mentioned. The most pronounced difference between MDD and non-MDD subjects is in the higher prevalence of *aggravation* and *visual aura* among the depressed individuals. While it is possible that these reflect real qualitative differences, alternative explanations should be considered. Especially in the case of 'aggravation', it is plausible that MDD patients tend to experience their headaches as more aggravating than non-depressed subjects as a result of their mood disorder. The increased prevalence of visual aura seems less likely to be a side effect of altered mood. One possible explanation for the difference is that the

questionnaire item that assessed aura does not measure aura sufficiently well. It could be that some patients in fact report some phenomenon related to depression, rather than real aura symptoms. An alternative explanation is that brain abnormalities associated with MDD might make an individual more susceptible to the phenomenon of cortical spreading depression, generally viewed as the mechanism underlying the migraine aura (24,25). This would not exclude the possibility that the migraine attack following the aura phase shows the same pattern of symptoms in MDD patients and controls.

Although the observed differences are small and subtle, they are significant (additional analyses in which the *aggravation* symptom was excluded from the model still produced significantly different profiles for the two groups). Therefore, we cannot exclude the possibility that these are true qualitative differences between depressed and non-depressed subjects. Also, it should be noted that qualitative similarity of migraine in MDD patients and controls is consistent with, but does not prove, a shared etiology.

Strengths and limitations

To our knowledge, this is the first study in which migraine symptomatology in MDD patients and controls is compared while taking into account expected differences in prevalence and severity. Figure 1 shows that more severely affected patients have a higher probability of all symptoms, but in particular *nausea/vomiting*, *photo-/phonophobia* and *aura*. Therefore, if prevalence and severity are not accounted for, a higher prevalence of these symptoms in MDD patients could be mistaken for a qualitative difference, whereas in reality it reflects a difference in the prevalence of severe migraine.

Another major strength of this study is the sample size, which is quite large compared to other studies of the comorbidity of migraine and depression. A total of 1816 clinically diagnosed MDD patients and 3428 controls selected for low risk of MDD participated, all of whom provided detailed information on migraine symptomatology.

At the same time, however, one potential limitation of this study is related to the sample size. Although the results of the LCAs in this study show considerable similarity to those we reported previously (10,11), in previous studies the best-fitting model was a 4-class rather than a three-class model. This is almost certainly a consequence of the larger sample sizes in these studies, which allowed the distinction of a fourth class. However, the additional class estimated in the previous studies reflected a less severe, non-migrainous form of headache on the same continuum of liability, and as noted in our previous twin studies, a three-class model captures most of the variance in migraine status that is captured by a four-class model. In addition, given that the current sample size (1816 cases and 3428 controls) is still quite large, any qualitative differences that can only be detected in larger samples would most likely be of little practical importance in distinguishing between 'pure migraine' and MDD-related migraine.

A second limitation concerns the questionnaire. Because no information was available on unilaterality of the headache, we cannot exclude the possibility that the frequency of unilateral headache may be different in MDD patients and controls. However, because patients were required to have at least two out of the three measured C criteria (see Table 1) to receive a migraine diagnosis, it is unlikely that the lack of information on unilateral headache has caused false-positive endpoint diagnoses. Indeed, the observed prevalence of migraine according to ICHD-II criteria was 3% (males) and 10% (females) in the low-risk control sample, and 4% (males) and 13% (females) in the total, unselected NTR sample ($N = 12303$), which is slightly lower than in other studies (26), possibly due to our somewhat conservative definition of migraine. Also, in the total, unselected NTR sample, 71% screened negative, which is relatively high compared to other studies (11). This suggests the screening procedure was somewhat strict. The screening question (''Do you ever experience headache attacks, for instance, migraine?'') did not specify a time frame; thus, attacks or symptoms that occur with a low frequency might not be reported. In addition, the phrasing might cause individuals who do not think their headache qualifies as migraine to respond negatively, even if they have some symptoms of migrainous headache. This would most likely result in an underestimate of the number of class 1 individuals. However, this issue is expected to affect prevalence estimates rather than estimates of qualitative migraine features.

Generalizability

The NTR is a population-based registry of unselected twin families. A non-response study found no evidence that participants' willingness to participate was related to migraine status (17). Whether findings in twins can be generalized to the singleton population can be tested by including data from the twins' siblings. In this study, twins had the same prevalence of each class of migrainous headache as their singleton siblings ($\chi^2(2)=1.617$, $p = .446$). The MDD cases in the NESDA study were selected from three different settings (community, primary care and specialized mental health care), to ensure that the resulting sample was representative of MDD in a wide range of settings, and included both milder and severe cases (14). To test whether the selection from different settings might have influenced the results,

symptom profiles were estimated separately for MDD patients from each setting. No qualitative differences in the symptom profiles were found between settings. Finally, to test whether treatment of MDD might cause any qualitative changes in migraine symptomatology, profiles were estimated separately for the MDD patients who received psychotherapy or treatment with antidepressants ($N = 871$) and those who did not ($N = 765$). The symptom profiles showed no significant qualitative differences related to treatment.

Conclusions and implications

Two important observations were made in this study. Firstly, the prevalence of *all* migraine symptoms is dramatically increased in MDD patients compared to non-depressed controls. This is also reflected in the fact that comparatively more MDD patients are classified as class 1 and 2 migrainous headache sufferers. Interestingly, the relationship between migraine and MDD appears to be stronger in males than in females.

A second important observation is that the migraine symptom profiles of MDD patients and non-depressed controls are very similar, suggesting that a similar disease process underlies migraine in both groups. We observed a slightly increased prevalence of *aggravation* and *aura* symptoms in the MDD group. However, the small size of the differences, combined with the large variability in symptoms among individual migraineurs indicate that looking at migraine symptoms alone does not support a distinction between ''pure'' migraine and migraine associated with depression.

This highlights the importance of collecting additional information besides those that make up the official diagnostic criteria for a given disorder. Information on the presence of comorbid MDD (symptoms) may be vital for any study investigating the etiology of migraine. This may also extend to other traits. Many disorders show comorbidity with migraine, in particular psychiatric disorders (depression, anxiety, bipolar disorder, phobias and panic disorder) (3,5,22), but also non-psychiatric disorders such as stroke, asthma, epilepsy, endometriosis and other chronic pain conditions (27–33). Similarly, depressed individuals show an increased prevalence of a variety of somatic symptoms, compared to non-depressed subjects (34), and a recent study demonstrated that migraine was an important predictor of other somatic symptoms in depressed subjects (35). In this context, it is interesting to mention the reported comorbidity between MDD and general chronic pain (36). Indeed, the MDD patients from the NESDA study reported a remarkably high frequency of pain symptoms, often at multiple sites (in the NTR these data were not available). While this might reflect a general tendency of depressed patients to more easily endorse questions regarding somatic complaints, it has been suggested that chronic pain might in fact be a symptom of depression (37). Although beyond the scope of the present study, this is a fundamental issue with important implications for research on migraine comorbidity. In conclusion, the collection of extensive and detailed information on comorbid disorders in studies of migraine could potentially improve our understanding of the etiology of these disorders and may contribute toward a more effective study of their underlying causes.

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