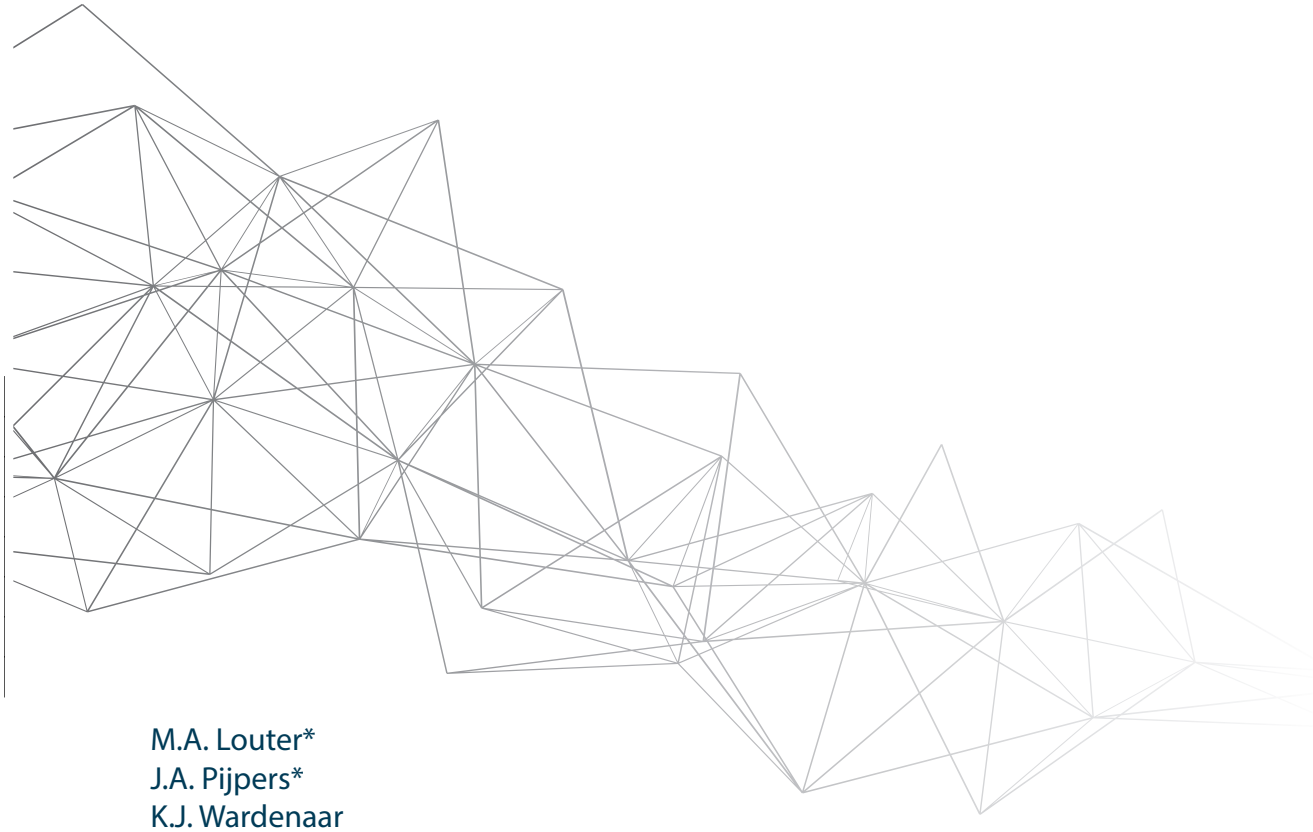
5 CHAPTER

Symptom dimensions of affective disorders in migraine patients



M.A. Louter*
J.A. Pijpers*
K.J. Wardenaar
E.W. van Zwet
A.M. van Hemert
F.G. Zitman
M.D. Ferrari
B.W. Penninx
G.M. Terwindt

Journal of Psychosomatic Research 2015 Nov;79(5):458-63
** both authors contributed equally to this manuscript*

Abstract

Objective
A strong association has been established between migraine and depression. However, this is the first study to differentiate in a large sample of migraine patients for symptom dimensions of the affective disorder spectrum.

Methods
Migraine patients (n = 3174) from the LUMINA (Leiden University Medical Centre Migraine Neuro-analysis Program) study and patients with current psychopathology (n = 1129), past psychopathology (n = 477), and healthy controls (n = 561) from the NESDA (Netherlands Study of Depression and Anxiety) study, were compared for three symptom dimensions of depression and anxiety. The dimensions –lack of positive affect (depression specific); negative affect (nonspecific); and somatic arousal (anxiety specific)– were assessed by a shortened adaptation of the Mood and Anxiety Symptom Questionnaire (MASQ-D30). Within the migraine group, the association with migraine specific determinants was established. Multivariate regression analyses were conducted.

Results
Migraine patients differed significantly ($p<0.001$) from healthy controls for all three dimensions: Cohen's *d* effect sizes were 0.37 for lack of positive affect, 0.68 for negative affect, and 0.75 for somatic arousal. For the lack of positive affect and negative affect dimensions, migraine patients were predominantly similar to the past psychopathology group. For the somatic arousal dimension, migraine patients scores were more comparable with the current psychopathology group. Migraine specific determinants for high scores on all dimensions were high frequency of attacks and cutaneous allodynia during attacks.

Conclusion
This study shows that affective symptoms in migraine patients are especially associated with the somatic arousal component.

Introduction

Migraine and depression are both rated among the top 20 of most disabling disorders by the World Health Organisation. (1) Previous studies showed that persons with migraine have a fivefold higher risk of first-onset major depression than persons without migraine. In addition, persons with a lifetime depressive disorder have a threefold higher risk of first-onset migraine than persons without a depression diagnosis. (2, 3) This bidirectional association suggests a shared aetiology, which is supported by several studies indicating shared genetic factors in migraine and depression. (4, 5) Besides depression, there is an association between anxiety disorders and migraine as well. (6) The economic impact of migraine is significantly compounded in patients with comorbid psychiatric conditions. (7) Understanding the mechanisms underlying the comorbidity is important in order to gain more insight into the mechanism of both migraine and depression/anxiety and to develop specific preventive treatments.

Previous studies in migraine defined depression using either categorical DSM-IV (Diagnostic and Statistical Manual of Mental Disorders) diagnoses or self-reported questionnaires. However, although DSM-IV categories are of great use in clinical practice, they have arbitrary boundaries, and show much overlap and comorbidity. Moreover, high heterogeneity of symptoms and severity within one diagnostic category is possible. (8) Depression and anxiety severity scales based on self-reported questionnaires also have limitations: two similar scores may indicate different clinical subtypes due to the heterogeneity of the covered range of symptoms as multidimensionality of symptomatology is not taken into account. Consequently, measuring affective disorders with these tools may provide suboptimal phenotyping for clinical and biological (e.g. genetic) research. Thus, in a research setting, it may be more appropriate to study dimensions of depressive and anxiety symptoms in migraine patients as these seem to reflect more homogeneous disease entities.

Several attempts have been made to develop a dimensional model for depression. Within a dimensional approach, a patient is described in terms of scores on a range of coexisting different symptom domains, and not in terms of presence or absence of psychopathology. (9) A well-known model is the tripartite model that accounts for the overlap between depression and anxiety. (10) In this model the broad symptom dimension of negative affect covers symptoms of general psychological distress (e.g. lack of concentration or pessimism). High negative affect has often been indicated as a central clinical feature of both anxiety and depression, accounting for the high rates of comorbidity. (11-14) The lack of positive affect covers anhedonic symptoms, which are mainly specific for depression. The somatic arousal dimension comprises symptoms of hyperarousal which are anxiety specific.

The aim of the present study is to investigate whether migraine patients are characterized by different symptom patterns of depressive and anxiety symptomatology compared with healthy controls, and persons with a current or past depression and/or anxiety disorder. Furthermore, we investigate which migraine specific characteristics are associated with the affective symptom dimensions of the tripartite model.

Methods

Study design and population

Four groups were differentiated for comparison: i) migraine patients, ii) healthy controls without psychopathology and without migraine, iii) persons with 'current psychopathology', a 6-month diagnosis of major depressive disorder, dysthymia or anxiety disorder and without migraine, and iv) persons with 'past psychopathology', a lifetime (but no current) diagnosis of major depressive disorder, dysthymia or anxiety disorder and without migraine.

Migraine patients were collected as a part of the Leiden University Medical Centre Migraine Neuro-analysis Programme (LUMINA) project, a well-defined web-based migraine population, the details of which are reported elsewhere. (15) The LUMINA project is an ongoing cohort study, designed to investigate migraine, its comorbidities, and its long-term course. Participants were Dutch adults aged 18 to 74 years with migraine with or without aura according to the International Classification of Headache Disorders (ICHD-III beta) criteria. (16) The LUMINA study population recruitment is still ongoing, but we included participants recruited between 2008 and 2011. Participants were recruited via nationwide public announcement, advertising in lay press and via the research website, inviting migraine patients to participate in migraine research (see supplementary). In addition, patients attending our dedicated headache clinic were also invited to participate in this survey. This latter group, however, comprises only 3.5% of the total LUMINA population. On the website, patients were asked to fill out a screening questionnaire that has been validated priorly. (17) Firstly, if patients fulfilled the screening criteria, they received a web-based extended migraine questionnaire, based on the ICHD-III beta criteria. (15, 16) This questionnaire was previously validated by a semi-structured telephone interview in 1038 patients who had filled out the extended migraine questionnaire. (15) The specificity of the questionnaire was 0.95. Participants without the needed internet skills could fill out the questionnaires on paper. Secondly, all applicable migraine patients were selected for a web-based questionnaire on symptoms of affective disorders. Patients were enrolled in this study after completion of the affective disorders questionnaire. The response rate to the depression questionnaire was 80%.

Healthy controls and patients with psychopathology were derived from the Netherlands Study of Depression and Anxiety (NESDA), which is an ongoing cohort study designed to investigate the long-term course and consequences of depressive and anxiety disorders. Participants were adults aged 18-65 recruited from community (19%), general practice (54%), and secondary mental health (27%) facilities. A total of 2981 participants, including persons with current or past depressive and/or anxiety disorders and healthy controls, were assessed at baseline between 2004 and 2007. Exclusion criteria for the NESDA study were inability to speak Dutch and a known clinical diagnosis of other psychiatric conditions, such as bipolar disorder, obsessive-compulsive disorder, severe addiction disorder, psychotic disorder or organic psychiatric disorder. A detailed description of the NESDA study design can be found elsewhere. (18) In summary, the baseline assessment was comprised of a face-to-face interview, including a standardized diagnostic psychiatric interview, a medical assessment, computer tasks, written questionnaires, and biological measurement. For the current study, migraine patients, identified through a screening migraine questionnaire largely in accordance to the ICHD-III beta criteria for migraine (described in detail elsewhere), were excluded from the NESDA population. (19)

The LUMINA project was approved by the medical ethics committee of the Leiden University Medical Centre. The NESDA research protocol was approved by the Ethical Committee of participating universities. All respondents provided written informed consent.

Measurements

In the NESDA study, the presence of psychiatric disorders was determined by using the Composite International Diagnostic Interview (CIDI, version 2.1). The CIDI is a standardized psychiatric diagnostic interview that follows the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria to establish diagnoses. The CIDI is a highly reliable and valid instrument for assessing depressive and anxiety disorders and was administered by specially trained research staff. (20) Psychopathology (major depressive disorder, dysthymia, anxiety disorder) status was categorized as follows: current diagnosis (i.e., past 6 months), past diagnosis (i.e., lifetime diagnosis but not in the past 6 months), controls (no lifetime diagnosis). In both the LUMINA and NESDA studies, a 30-item adaptation of the Mood and Anxiety Symptoms Questionnaire (MASQ-D30) was used to measure the tripartite dimensions of depression. On the MASQ-D30, participants were asked to rate to what extent in the past week they had experienced 'feelings, sensations, problems and experiences that people sometimes have' on a 5-point scale, with 1 being 'not at all' and 5 being 'extremely'.

The three 10-item subscales are 'general distress' (lack of positive affect), 'anhedonic depression' (negative affect) and 'anxious arousal' (somatic arousal). The MASQ-D30 scales showed adequate psychometric characteristics and showed good reliability and validity within the NESDA study. (21)

In the LUMINA population, we predefined migraine specific characteristics to be examined: migraine subtype (migraine with or without aura), frequency (migraine days per year), and cutaneous allodynia. Cutaneous allodynia, the perception of pain in response to non-noxious stimuli to the normal skin, is a common feature accompanying migraine attacks. A significant part of migraine patients experience an increased sensitivity of the skin for common daily activities during attacks, such as combing of hair, taking a shower, touching the periorbital skin, shaving, or wearing earrings during migraine attacks. Cutaneous allodynia was measured using a validated questionnaire. (22) These migraine specific characteristics are shown to be associated with depression. (23, 24)

Data analysis and statistics

Baseline characteristics were reported as mean ± standard deviations (SD) or percentages. Analysis of covariance (ANCOVA) models were used to test the association between the four different groups and MASQ-D30 symptom profiles, adjusting for gender and age. Post-hoc analyses were run in case of significant findings, performing ANCOVA analysis to test for differences between the migraine group and the three remaining groups. Results were presented as *p*-values with Cohen's *d* (the difference between the means, divided by the pooled standard deviation) as a measure of effect size. Secondary analyses were performed in the migraine population, using multivariate linear regression, testing for the association between general and migraine specific determinants and the three dimensions of affective disorders. Results were presented as *p*-values and *B*-values with 95% confidence intervals. For the primary analyses, we measured three outcomes (the three subscales of the MASQ-D30 questionnaire). Therefore, using Bonferoni correction for multiple testing, *p*-values <0.017 (0.05/3) were considered as statistically significant. Secondary, hypothesis generating analyses, were performed without correction for multiple testing. All analyses were performed using SPSS 20.0 (SPSS Inc., IBM, USA).

Results

Of 2981 NESDA participants, 454 fulfilled the criteria for migraine, and 360 lacked MASQ-D30 data and were excluded for analysis. As a result, the total amounts of participants were 1129 with current psychopathology, 477 with past psychopathology, and 561 healthy controls. A total of 3174 migraine patients with

sufficient data on migraine characteristics and MASQ-D30 data were extracted from the LUMINA database. The total study flow is depicted in figure 1.

Baseline characteristics for the four groups are shown in table 1. Because of differences in gender distribution and age distribution between the four groups ($p < 0.001$), all analyses were corrected for gender and age. As the LUMINA and NESDA cohorts had different assessments of educational level the analyses were not corrected for that socio-demographic characteristic.

In the first analysis (table 2) the four groups (migraine patients, healthy controls, persons with past psychopathology, and persons with current psychopathology) were compared using a multivariate linear regression analysis with adjustment for age and gender. There was a significant difference ($p<0.001$) between the four subgroups for the three symptoms dimensions (lack of positive affect (depression specific); negative affect (nonspecific); and somatic arousal (anxiety specific)). Further pairwise comparison with migraine as reference group is depicted in figure 2. Migraine patients were significantly different ($p<0.001$) for all comparisons to the two psychopathology groups and healthy controls, except for the lack of positive affect compared with the past psychopathology group. In figure 2, differences between the groups are displayed as Cohen's *d*, a measure of effect size, showing that scores on the lack of positive affect (Cohen's $d=0.07$) and negative affect (Cohen's $d=0.30$) dimensions for migraine patients are most closely related to the past psychopathology group. For the somatic arousal subscale scores migraine patients are closer related to current psychopathology (Cohen's $d=0.25$).

Within the group of migraine patients (n=3174), general and migraine specific determinants for the three subscales of affective disorders were analysed using multivariate linear regression (table 3). Age was significantly associated with lack of positive affect and negative affect. Gender was significantly associated with somatic arousal. Migraine frequency and cutaneous allodynia, but not migraine subtype, were associated with all three symptom dimensions of the affective disorder questionnaire.

Discussion

This is the first study differentiating in a large sample of migraine patients for symptom dimensions of depression and anxiety. In comparison with healthy controls and persons with past or current psychopathology, affective disorder symptoms in migraine are specifically associated with higher scores on the dimension somatic arousal which covers symptoms of hyperarousal. Furthermore, the association between MASQ-D30 scores and migraine frequency, which can be considered as an indication of migraine severity, is the strongest on the somatic

arousal subscale. Besides migraine frequency, we show that cutaneous allodynia is associated with higher scores on all three symptom dimensions as well.

Our finding that migraine is particularly associated with the somatic arousal dimension is in accordance with that of several other somatic disorders. Association studies investigating the relationship of depression with chronic diseases like diabetes, obesity, and cardio-vascular disease often show that somatic-affective symptoms of depression rather than cognitive-affective symptoms are related to somatic disease (25-28). Therefore, it is often hypothesized that the association between a somatic disease and depression is primarily through the somatic-affective dimension of depression, the so-called somatic depression (29, 30).

One might also argue that part of the comorbidity between migraine and affective disorders could be due to overlapping symptomatology. Some of the characteristic features of migraine attacks, such as nausea, loss of energy, anhedonia, and sleep disturbances, could lead to misclassification of depressive disorder in migraine patients. However, the association of migraine and depression is still present when questionnaires focusing on the non-somatic aspects of depression are applied, such as the Hospital Anxiety and Depression Scale) (24). Furthermore, the current study clearly shows that the symptom profile of affective disorders in migraine patients differs from healthy controls for all three dimensions of the MASQ-D30 questionnaire, not only for the somatic arousal dimension. Therefore, our study shows that affective disorders in migraine patients cannot be fully explained by somatic depression or overlapping symptomatology. However, our study does suggest an even stronger comorbidity between migraine and symptoms of anxiety, than between migraine and symptoms of depression per se. This is particularly interesting, since most studies hitherto focused on the comorbidity between migraine and depression, whilst the comorbidity of migraine and anxiety is a largely unexplored area. Larger and prospective studies on the comorbidity of migraine and anxiety disorders are necessary to establish the exact magnitude of this comorbidity.

Our study shows that anxiety arousal might be the corresponding component, but the underlying mechanism should be further investigated.

Because the co-occurrence between migraine and affective disorders is not fully explained by mechanisms such as somatic depression or overlapping symptomatology we argue that there is a true comorbidity between migraine and depression. Additionally, previous studies showed a bidirectional relationship, in which the risk for depression is five times increased in migraine patients, and vice versa, the risk for migraine is three times increased in patients with depression (2, 3). This bidirectional association suggests shared underlying mechanisms, presumably shared genetic factors (4, 5). However, further genetic research did

not yet result in clues which exact genes are involved in this association. The current study stresses the importance of a dimensional approach for depression in migraine in a research setting, as the current concept of depression probably is too heterogeneous for detecting genetic variants involved in this association. Using subgroups of migraine patients, based on the tripartite model of depression and anxiety, may be warranted in further genetic research on the comorbidity of migraine and affective disorders.

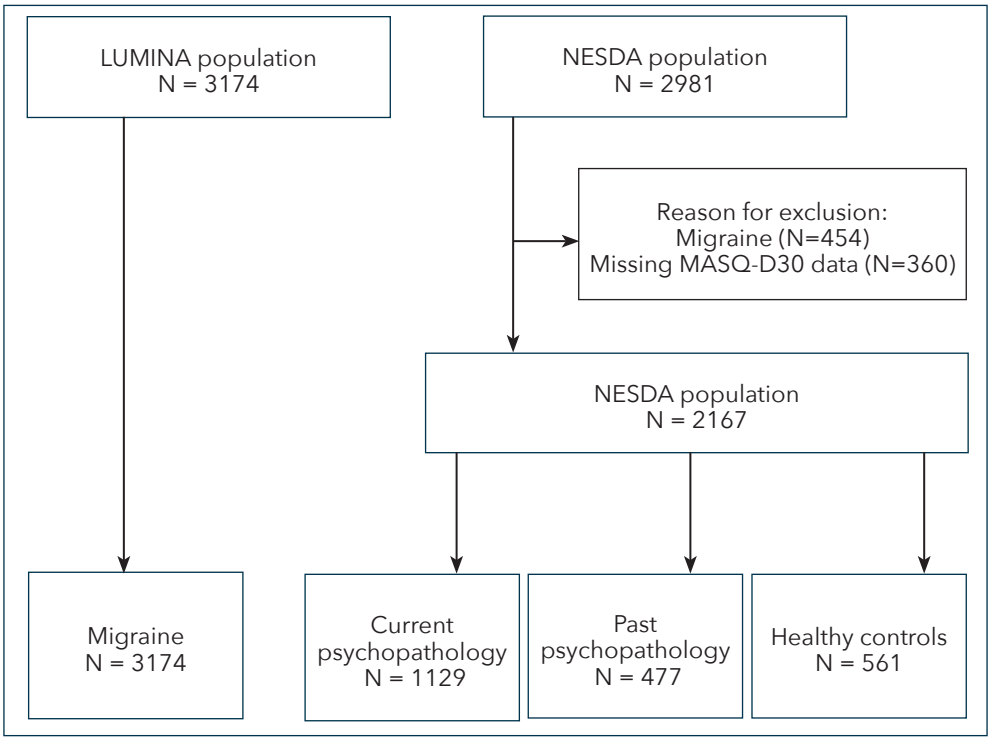
Comorbid depression in migraine is an important predictor of substance dependence and is common in chronic migraine patients, in particular in those with overuse of acute headache medication (31). Thus a triad between migraine chronification, depression and medication overuse has been suggested (32-34). In this triad, cutaneous allodynia plays a role. Allodynia, the perception of pain in response to non-noxious stimuli to the normal skin, is a common feature accompanying migraine attacks. Previously, we showed that depression and high migraine attack frequency (as a marker of chronification) are independently associated with cutaneous allodynia (23). The present study supports this finding and shows that both cutaneous allodynia and high migraine frequency, are associated with all three symptom dimensions of affective disorders, covering general distress as well as anxiety and depression specific symptoms.

The strengths of this study are the large sample size, the well-defined migraine status in the LUMINA population, the well-defined psychopathology status in the NESDA population, and the well-defined healthy control population from NESDA. Most importantly, this is the first study focusing on the different symptom dimensions of affective disorders in migraine patients. Possible limitations include the fact that we compare two different cohorts, in which data was collected in different ways and time periods.

In conclusion, we found that migraine patients, without taking their history of psychopathology into account, differ significantly from healthy controls on all three dimensions of affective disorders. The strongest difference is seen on the somatic-affective component which is suggestive of increased anxiety. Using subgroups of migraine patients, based on the tripartite model of affective disorders, may be warranted in further biological research on the comorbidity of migraine, anxiety and depression.

Figures and tables

Figure 1: Study flow



LUMINA = Leiden University Medical Centre Migraine Neuro-analysis Program
NESDA = Netherlands Study of Depression and Anxiety
MASQ-D30 = Mood and Anxiety Symptoms Questionnaire

Table 1: Descriptive characteristics of the LUMINA and NESDA sample

	LUMINA	NESDA		
	Migraine patients N = 3174	Current psycho-pathology patients N = 1129	Past psycho-pathology patients N = 477	Healthy controls N = 561
Gender (% female)	85.6%	64.0%	68.1%	59.7%
Age (years± SD)	43.2 ± 11.7	42.7 ± 12.6	44.6 ± 13.2	41.5 ± 14.9
NESDA population characteristics				
Current MDD (without anxiety disorder)	.	25.4%	.0%	.0%.
Current anxiety disorder (without MDD)	.	33.1%	.0%	.0%
Current MDD & anxiety disorder	.	41.5%	.0%	.0%
Lifetime MDD (without anxiety disorder)	.	17.4%	45.7%	.0%
Lifetime anxiety disorder (without MDD)	.	16.7%	18.9%	.0%
Lifetime MDD & anxiety disorder	.	65.9%	35.4%	.0%
LUMINA population characteristics				
Migraine with aura	38.2%	.		
Migraine without aura	61.8%	.	.	.
Mean age at onset (years ± SD)	19.3 ± 10.7	.	.	.
			.	.
Migraine attack frequency (migraine days/year)		.		
1-2	5.1%	.	.	.
3-6	10.1%	.	.	.
7-12	16.7%	.	.	.
13-54	46.1%	.	.	.
54+	22.0%	.	.	.
Cutaneous allodynia	70.0%		.	.

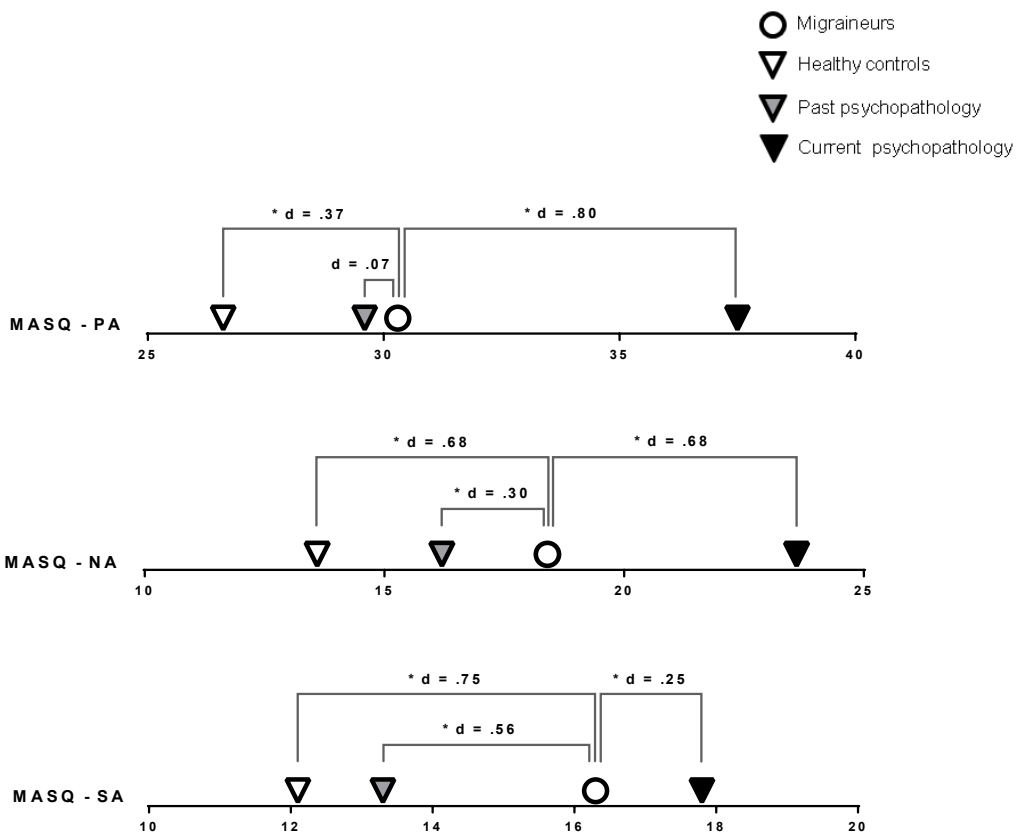
MDD = Major depressive disorder

Table 2: Mean MASQ-D30 scores in the 4 study cohorts, adjusted for age and gender.

	LUMINA	NESDA			
	Migraine patients N = 3174	Current psychopathology patients N = 1129	Past psychopathology patients N = 477	Healthy controls N = 561	P-value (ANCOVA)
MASQ-PA	30.3 ± 9.0	37.5 ± 9.0	29.6 ± 8.9	26.6 ± 9.0	**<0.001**
MASQ-NA	18.4 ± 7.2	23.6 ± 7.1	16.2 ± 7.1	13.6 ± 7.1	**<0.001**
MASQ-SA	16.3 ± 5.4	17.8 ± 5.4	13.3 ± 5.3	12.1 ± 5.4	**<0.001**

MASQ-PA= positive affect subscale
MASQ-NA = negative affect subscale
MASQ-SA = somatic arousal subscale

Figure 2: effect sizes of the difference between migraine patients compared with healthy controls, past psychopathology and current psychopathology.



Cohen's d indicates a small effect if it is around 0.2, a moderate effect if it is around 0.5 and a large effect if it is greater than 0.8. * indicates $p<0.001$

MASQ-PA= positive affect subscale
MASQ-NA = negative affect subscale
MASQ-SA = somatic arousal subscale

Table 3: Determinants of MASQ-D30 subscales in a migraine population (n=3174)

	MASQ-PA		MASQ-NA		MASQ-SA	
	B (95% CI)	p-value	B (95% CI)	p-value	B (95% CI)	p-value
General determinants						
Age	**0.05 (0.02 – 0.08)**	**<0.001**	**-0.06 (-0.08 - -0.04)**	**<0.001**	0.01 (-0.002 – 0.03)	0.08
Gender (Female vs Male)	0.24 (-0.70 – 1.18)	0.62	0.35 (-0.37 – 1.07)	0.34	**0.83 (0.29 – 1.38)**	**0.003**
Migraine specific determinants						
Migraine subtype (without aura vs with aura)	0.19 (-0.48 – 0.86)	0.58	0.27 (-0.24 – 0.78)	0.30	-0.33 (-0.72 – 0.05)	0.09
Migraine frequency (migraine days/year)						
3-6 vs 1-2	0.04 (-1.69 – 1.78)	0.96	0.41 (-0.92 – 1.73)	0.55	**1.03 (0.03 – 2.03)**	**0.04**
7-12 vs 1-2	1.40 (-0.21 – 3.02)	0.09	0.55 (-0.68 – 1.78)	0.38	**1.49 (0.56 – 2.42)**	**0.002**
13-54 vs 1-2	**1.65 (0.15 – 3.15)**	**0.03**	0.92 (-0.22 – 2.06)	0.11	**1.74 (0.88 – 2.60)**	**<0.001**
54+ vs 1-2	**4.18 (2.60 – 5.75)**	**<0.001**	**2.64 (1.44 – 3.85)**	**<0.001**	**3.30 (2.39 – 4.21)**	**<0.001**
Cutaneous allodynia (yes vs no)	**2.00 (1.29 – 2.72)**	**<0.001**	**1.80 (1.26 – 2.35)**	**<0.001**	**2.04 (1.63 – 2.45)**	**<0.001**

MASQ-PA= positive affect subscale
MASQ-NA = negative affect subscale
MASQ-SA = somatic arousal subscale

References

1. (WHO) WHO. The Global Burden of Disease2004 2004.
2. Breslau N, Lipton RB, Stewart WF, Schultz LR, Welch KM. Comorbidity of migraine and depression: investigating potential etiology and prognosis. Neurology. 2003;60(8):1308-12.
3. Breslau N, Schultz LR, Stewart WF, Lipton RB, Lucia VC, Welch KM. Headache and major depression: is the association specific to migraine? Neurology. 2000;54(2):308-13.
4. Schur EA, Noonan C, Buchwald D, Goldberg J, Afari N. A twin study of depression and migraine: evidence for a shared genetic vulnerability. Headache. 2009;49(10):1493-502.
5. Stam AH, de VB, Janssens AC, Vanmolkot KR, Aulchenko YS, Henneman P, et al. Shared genetic factors in migraine and depression: evidence from a genetic isolate. Neurology. 2010;74(4):288-94.
6. Victor TW, Hu X, Campbell J, White RE, Buse DC, Lipton RB. Association between migraine, anxiety and depression. Cephalalgia. 2010;30(5):567-75.
7. Elston LJ, Moon C, Leotta C, Kolodner K, Poisson L, Lipton RB. The medical care utilization and costs associated with migraine headache. J GenIntern Med. 2004;19(10):1005-12.
8. Widiger TA, Samuel DB. Diagnostic categories or dimensions? A question for the Diagnostic And Statistical Manual Of Mental Disorders--fifth edition. JAbnormPsychol. 2005;114(4):494-504.
9. Luppino FS, van Reedt Dortland AK, Wardenaar KJ, Bouvy PF, Giltay EJ, Zitman FG, et al. Symptom dimensions of depression and anxiety and the metabolic syndrome. PsychosomMed. 2011;73(3):257-64.
10. Clark LA, Watson D. Tripartite model of anxiety and depression: psychometric evidence and taxonomic implications. JAbnormPsychol. 1991;100(3):316-36.
11. Mineka S, Watson D, Clark LA. Comorbidity of anxiety and unipolar mood disorders. AnnuRevPsychol. 1998;49:377-412.
12. Krueger RF. The structure of common mental disorders. ArchGenPsychiatry. 1999;56(10):921-6.
13. Vollebergh WA, Iedema J, Bijl RV, de GR, Smit F, Ormel J. The structure and stability of common mental disorders: the NEMESIS study. ArchGenPsychiatry. 2001;58(6):597-603.
14. Watson D. Rethinking the mood and anxiety disorders: a quantitative hierarchical model for DSM-V. JAbnormPsychol. 2005;114(4):522-36.
15. van Oosterhout WP, Weller CM, Stam AH, Bakels F, Stijnen T, Ferrari MD, et al. Validation of the web-based LUMINA questionnaire for recruiting large cohorts of migraineurs. Cephalalgia. 2011.
16. The International Classification of Headache Disorders, 3rd edition (beta version). Cephalalgia. 2013;33(9):629-808.
17. Launer LJ, Terwindt GM, Ferrari MD. The prevalence and characteristics of migraine in a population-based cohort: the GEM study. Neurology. 1999;53(3):537-42.
18. Penninx BW, Beekman AT, Smit JH, Zitman FG, Nolen WA, Spinhoven P, et al. The Netherlands Study of Depression and Anxiety (NESDA): rationale,

objectives and methods. IntJMethods PsychiatrRes. 2008;17(3):121-40.
19. Ligthart L, Penninx BW, Nyholt DR, Distel MA, de Geus EJ, Willemsen G, et al. Migraine symptomatology and major depressive disorder. Cephalalgia. 2010;30(9):1073-81.
20. Wittchen HU. Reliability and validity studies of the WHO--Composite International Diagnostic Interview (CIDI): a critical review. JPsychiatrRes. 1994;28(1):57-84.
21. Wardenaar KJ, van VT, Giltay EJ, de BE, Penninx BW, Zitman FG. Development and validation of a 30-item short adaptation of the Mood and Anxiety Symptoms Questionnaire (MASQ). Psychiatry Res. 2010;179(1):101-6.
22. Lipton RB, Bigal ME, Ashina S, Burstein R, Silberstein S, Reed ML, et al. Cutaneous allodynia in the migraine population. AnnNeurol. 2008;63(2):148-58.
23. Louter MA, Bosker JE, van Oosterhout WP, van Zwet EW, Zitman FG, Ferrari MD, et al. Cutaneous allodynia as a predictor of migraine chronification. Brain. 2013.
24. Louter MA, Wardenaar KJ, Veen G, van Oosterhout WP, Zitman FG, Ferrari MD, et al. Allodynia is associated with a higher prevalence of depression in migraine patients. Cephalalgia. 2014;34(14):1187-92.
25. Michal M, Wiltink J, Kirschner Y, Wild PS, Munzel T, Ojeda FM, et al. Differential associations of depressive symptom dimensions with cardio-vascular disease in the community: results from the Gutenberg health study. PLoSOne. 2013;8(8):e72014.
26. Wiltink J, Michal M, Wild PS, Zwiener I, Blettner M, Munzel T, et al. Associations between depression and different measures of obesity (BMI, WC, WHtR, WHR). BMCPsychiatry. 2013;13:223.
27. Wiltink J, Michal M, Wild PS, Schneider A, Konig J, Blettner M, et al. Associations between depression and diabetes in the community: do symptom dimensions matter? Results from the Gutenberg Health Study. PLoSOne. 2014;9(8):e105499.
28. Marijnissen RM, Bus BA, Holewijn S, Franke B, Purandare N, de GJ, et al. Depressive symptom clusters are differentially associated with general and visceral obesity. JAmGeriatrSoc. 2011;59(1):67-72.
29. Lamers F, de JP, Nolen WA, Smit JH, Zitman FG, Beekman AT, et al. Identifying depressive subtypes in a large cohort study: results from the Netherlands Study of Depression and Anxiety (NESDA). JClinPsychiatry. 2010;71(12):1582-9.
30. Penninx BW, Milaneschi Y, Lamers F, Vogelzangs N. Understanding the somatic consequences of depression: biological mechanisms and the role of depression symptom profile. BMCMed. 2013;11:129.
31. Vieira DS, Naffah-Mazacoratti MG, Zukerman E, Senne Soares CA, Alonso EO, Faulhaber MH, et al. Cerebrospinal fluid GABA levels in chronic migraine with and without depression. Brain Res. 2006;1090(1):197-201.
32. Radat F, Sakh D, Lutz G, el AM, Ferreri M, Bousser MG. Psychiatric comorbidity is related to headache induced by chronic substance use in migraineurs. Headache. 1999;39(7):477-80.
33. Mercante JP, Peres MF, Guendler V, Zukerman E, Bernik MA. Depression in chronic migraine: severity and clinical features. Arq Neuropsiquiatr. 2005;63(2A):217-20.

34. Bigal ME, Lipton RB. Modifiable risk factors for migraine progression. Headache. 2006;46(9):1334-43.