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Research Submissions

Migraine Headaches and Mood/Anxiety Disorders in the ELSA Brazil

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Objective.—To describe the relationship between mood/anxiety disorders and migraine headaches emphasizing the frequency of episodes based in a cross-sectional analysis in the Brazilian Longitudinal Study of Adult Health.

Background.—It has been suggested that frequency of migraine headaches can be directly associated with the presence of psychiatric disorders.

Methods.—Migraine headaches (International Headache Society criteria) was classified as <1×/month, 1×/month-1×/week, 2-6×/week, and daily. Psychiatric disorders using the Clinical Interview Schedule – Revised were classified in 6 categories: common mental (CMD), major depressive (MDD), generalized anxiety (GAD), panic, obsessive-compulsive (OCD), and mixed anxiety and depressive (MADD) disorders. We performed multivariate logistic models adjusted for age, race, education, marital status, income, and use of selective serotonin reuptake inhibitors.

Results.—In our sample, 1261 presented definite migraine and 10,531 without migraine headaches (reference). Our main result was an increase in the strength of association between migraine and MDD as frequency of migraine increased for all sample: odds ratio of 2.14 (95% confidence interval [CI] 1.33-3.43) for <1 episode of migraine/month to 6.94 (95% CI 4.20-11.49) for daily headaches for all sample. Significant associations with migraine were also found for GAD, OCD, MADD, and CMD for total sample: MDD, GAD, OCD, MADD, and CMD for women, and MADD and CMD for men. Among men with daily migraine complaint, we found a significant association between migraine and OCD after correction for multiple comparisons (odds ratio 29.86 [95% CI 4.66-191.43]). Analyzing probable and definite migraine cases together, we replicated the findings in a lower magnitude.

Conclusions.—The increase in migraine frequency was associated with progressively higher frequencies of having mood/anxiety disorders in all samples suggesting for some psychiatric disorders a likely dose-response effect especially for women.

Key words: migraine, mood disorder, epidemiology

Abbreviations: CI confidence interval, CIS-R Clinical Interview Schedule – Revised, CMD common mental disorder, ELSA-Brasil Brazilian Longitudinal Study of Adult Health, ICD-10 International Classification of Diseases, IHS International Headache Society, GAD general anxiety disorder, MADD mixed anxiety and depressive disorder, MDD major depressive disorder, OCD obsessive-compulsive disorder, OR odds ratio

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Background.—It has been suggested that mood disorders and anxiety are approximately 2-3 times more prevalent in migraineurs compared with general population.[1-4] Longitudinal studies have demonstrated a causal relationship between mood and anxiety disorders and migraine with differing results.[5-7] Breslau et al found a bidirectional relationship between major depression and migraine.[5] A retrospective cohort study described migraine association with later development of major depressive episodes but did not provide strong causal evidence in the other direction.[6] In the Baltimore study, there were no associations between previous history of affective disorders and incident migraine headaches.[7] Besides that, some individuals with mood disorders are more likely to have worsening prognosis as seen in the progression from episodic migraine to chronic migraine.[8] It has been suggested that an increase of migraine frequency is directly associated to an increase in the risk of having mood/anxiety disorders and anxiety. According to Ashina et al, individuals with moderate, moderately severe, and severe depression presented a progressive increase in the frequency of chronic migraine compared with those with no or mild depression.[8]

Objectives.—Thus, our aim was to describe the relationship between mood/anxiety disorders and migraine headaches emphasizing the frequency of episodes based on the baseline data of the Brazilian Longitudinal Study of Adult Health (ELSA-Brasil). The ELSA-Brasil, a prospective cohort of 15,105 civil servants including both men and women aged 35-74 years, is a very unique opportunity to explore associations between migraine, mood, and anxiety disorders using variables accrued by standardized tools applied at baseline.

METHODS

Study Design, Settings, and Participants.—This is a cross-sectional analysis using data from the baseline of ELSA-Brasil, an ongoing prospective multicenter study involving 6 sites in 3 macroregions of Brazil (Northeast, Southeast, and the South). Baseline assessment occurred from 2008 to 2010, and it was designed to investigate factors associated to the development and progression of cardiovascular diseases and diabetes. All active or retired employees of the 6 institutions aged 35-74 years were eligible for the study. Exclusion criteria were current or recent (<4 months prior to the first interview) pregnancy, intention to quit working at the institution in the near future, severe cognitive or communication impairment, and, if retired, residence outside of a study center's corresponding metropolitan area. The sample size estimation was based on the main study outcomes – type 2 diabetes and myocardial infarction. Further details of cohort are described elsewhere.[9] Approvals from all Institutional Review Boards were guaranteed.

Outcomes.—*Migraine Definition.*—All participants who answered "yes" to the question "In the last 12 months, did you have a headache?" at the ELSA-Brasil baseline evaluation were invited to answer a detailed headache questionnaire based on the International Headache Society criteria (IHS-2004).[10] This questionnaire was validated in Brazil,[11] and has been used in previous studies.[12,13]

Briefly, this questionnaire investigates pain frequency, duration, quality, location, intensity, triggering, and accompanying symptoms, such as nausea or vomiting, and the presence of aura. Based on this questionnaire, we classified participants as having definite migraine if they fulfilled criteria for IHS codes 1.1 (migraine without aura) or 1.2 (migraine with aura). Regarding the frequency of migraine attacks, we classified participants according to 4 levels of episode frequency: less than once per month, 1 per month to 1 per week, 2-6 per week, and daily. We classified individuals who answered "yes" to the

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question about headache but did not fulfill criteria for migraine and individuals who answered "no" to the question about headache as non-migraine subgroup, and they were the reference group for all analyses.

Mood/Anxiety Disorders Definition.—Psychiatric disorders were investigated by an adapted Brazilian-Portuguese version of the Clinical Interview Schedule – Revised (CIS-R) applied by trained interviewers.[14] The CIS-R is a structured interview for measurement and diagnosis of non-psychotic psychiatric morbidity in community. It was developed by Lewis et al[15] specifically to be used in community and primary care, by being a short and straightforward questionnaire. Importantly, lay interviewers are as reliable as psychiatrist in using CIS-R for performing mental diagnosis, being a suitable instrument to be used in epidemiological studies.

The complete CIS-R version includes 14 sections covering symptoms of depression and anxiety: obsessions, compulsions, panic, phobias, anxiety, worry, worry about physical health, depression, depressive ideas, irritability, fatigue, concentration, sleep, and somatic symptoms.[15] The CIS-R also yields International Classification of Diseases (ICD-10) diagnoses. The relevant symptoms reported by the participant are grouped to form ICD-10 diagnoses. Here, we investigated the association between migraine headache and psychiatric morbidity separate as follow: major depressive disorder (MDD, F32.xx), general anxiety disorder (GAD, F41.1), panic disorder (F41.0), obsessive-compulsive disorder (OCD, F42), and mixed anxiety and depressive disorder (MADD, F41.2) in participants with symptoms of anxiety and depression that did not fulfill isolated criteria for MDD or GADs. CIS-R can also be computed as a score with a range from 0 to 57. People are classified as having common mental disorders (CMDs) if they present a score ≥12.

Statistics.—All main analyses were done using definite migraine. Baseline characteristics were described according to headache frequency (less than once per month, 1 per month to 1 per week, 2-6 per week and daily) using the chi-square test for categorical variables and analysis of variance with post-hoc test of Bonferroni for continuous variables whenever applicable. We also calculated odds ratios (ORs) for the association of migraine with MDD, GADs, panic disorders, OCDs, MADD, and CMDs using the non-migraine headache subgroup as reference. Non-migraine headache subgroups included people with no headache and people with non-migraine headaches. We performed crude and multivariate multinomial logistic regression analyses adjusted by age, gender, race, educational level, marital status, family income, and use of selective serotonin reuptake inhibitors.

We ran gender interaction analysis in adjusted multinomial logistic models. Because this is a secondary analysis, which includes many different regressions, we have chosen *Bonferroni* correction to adjust *P* values for multiple comparisons. We also repeat all the analyses grouping together definite and probable migraine (all IHS criteria but 1) using non-migraine group as the reference and changing reference group only to people with no headache. Because it is expected that there is a higher frequency of definite migraine and of all psychiatric disorders in women compared with men, we performed all logistic models stratified by gender.

For all analyses, *P* values less than .05 were also considered as significant. The statistical analyses were performed with the statistical software SPSS version 19.0 (IBM, Armonk, NY, USA).

RESULTS

In the present study, from the 15,105 participants, 177 were excluded from the analysis because of missing information on the CIS-R or in the migraine questionnaire. Of the 14,928, 4458 reported no headache, 6073 non-migraine headaches, 3136 probable migraine, and 1261 definite migraine. Frequency of definite migraine headaches was 8.4% and of probable migraine, 21.0%. All main analyses were based on the comparison between non-migraine and definite migraine comprising in total 11,792 participants.

We observed the following frequencies of mental disorders according to gender in participants with migraine: 10.8% for women vs 6.3% for men (*P* = .11) for MDD; 27.4% for women vs 18.9% for men (*P* = .03) for generalized anxiety disorder; 6.2% for women vs 5.7% for men (*P* = .007) for OCD; 21.3%

for women vs 20.8% for men for MADD ($P = .004$); and 53.9% for women vs 41.5% for men ($P = .005$) for CMDs.

Baseline characteristics according to migraine status are shown in Table 1. As expected, migraine was more frequent among younger participants (≤54 years old) and females, and in the lower income categories regardless of migraine frequency. Overall, daily migraine sufferers were more frequently single, black (self-reported race), and had a family income up to US$ 1284 per month (Table 1). Accordingly, an increase in the migraine frequency was associated with an increase in the frequency of mood/anxiety disorders. Moreover, the frequency of participants

Table 1.—Baseline Characteristics of 11,792 Participants From the ELSA-Brasil Cohort, According to Frequency of Migraine Headaches

		Migraine Frequency			
Characteristics	No Migraine N = 10,531	<1×/Month N = 291	1×/Month-1×/Week N = 573	2-6×/Week N = 298	Daily N = 99
Mean age (years) (±SD)					
Age strata (%)					
35-44 years	2099 (19.9%)	61 (21.0%)	190 (33.2%)	90 (30.2%)	23 (23.2%)
45-54 years	3884 (36.9%)	142 (48.8%)	285 (49.7%)	147 (49.3%)	38 (38.4%)
55-64 years	3167 (30.1%)	69 (23.7%)	88 (15.4%)	49 (16.4%)	35 (35.4%)
65-74 years	1381 (13.1%)	19 (6.5%)	10 (1.7%)	12 (4.0%)	3 (3%)
Gender (%)					
Male	5769 (54.8%)	49 (16.8%)	68 (11.9%)	35 (11.7%)	7 (7.1%)
Female	4762 (45.2%)	242 (83.2%)	505 (88.1%)	263 (88.3%)	92 (92.9%)
Race (%)					
White	5488 (52.8%)	129 (44.6%)	309 (53.9%)	153 (51.3%)	26 (26.3%)
Brown	2900 (27.9%)	84 (29.1%)	151 (26.4%)	82 (27.5%)	33 (33.3%)
Black	1631 (15.7%)	66 (22.8%)	92 (16.1%)	49 (16.4%)	36 (36.4%)
Other (Yellow or Indian)	379 (3.6%)	10 (3.5%)	17 (3.0%)	12 (4.0%)	3 (3%)
Years of education (%)					
Bellow high school	1437 (13.6%)	35 (12.0%)	34 (5.9%)	31 (10.4%)	21 (21.2%)
High school	3450 (32.8%)	123 (42.3%)	209 (36.5%)	143 (48.0%)	61 (61.6%)
At least college	5644 (53.6%)	133 (45.7%)	330 (57.6%)	124 (41.6%)	17 (17.2%)
Marital status (%)					
Single	3432 (32.6%)	122 (41.9%)	222 (38.7%)	117 (39.3%)	54 (54.5%)
Married	7099 (67.4%)	169 (58.1%)	351 (61.3%)	181 (60.7%)	45 (45.5%)
Family income (%)					
≤USD 1284	2690 (25.7%)	91 (31.4%)	153 (26.7%)	101 (34.0%)	54 (54.5%)
USD 1285-3319	4485 (42.8%)	140 (48.3%)	271 (47.3%)	140 (47.1%)	37 (37.4%)
≥USD 3320	3310 (31.6%)	59 (20.3%)	149 (26.0%)	56 (18.9%)	8 (8.1%)
Psychiatric comorbidities† (%)					
Major depressive disorder	259 (2.5%)	21 (7.2%)	45 (7.9%)	39 (13.1%)	24 (24.2%)
Panic disorder	83 (0.8%)	7 (2.4%)	6 (1.0%)	4 (1.3%)	3 (3.1%)
Generalized anxiety disorder	974 (9.3%)	68 (23.6%)	131 (23.1%)	92 (31.2%)	41 (41.8%)
Obsessive-compulsive disorder	140 (1.3%)	12 (4.1%)	32 (5.6%)	24 (8.1%)	9 (9.2%)
Mixed anxiety-depressive disorder	1061 (10.1%)	54 (18.6%)	116 (20.2%)	76 (25.5%)	22 (22.2%)
Common mental disorder	2027 (19.2%)	130 (44.7%)	267 (46.6%)	186 (62.4%)	77 (77.8%)
Number of psychiatric comorbidities (%)					
None	8118 (77.8%)	148 (51.6%)	277 (48.9%)	102 (34.2%)	18 (18.4%)
1	350 (3.4%)	13 (4.5%)	31 (5.5%)	13 (4.4%)	6 (6.1%)
2	1751 (16.8%)	104 (36.2%)	218 (38.5%)	144 (48.3%)	55 (56.1%)
3 or more	210 (2.0%)	22 (7.7%)	40 (7.1%)	35 (11.9%)	19 (19.4%)

†Mood disorders and anxiety were assessed by the Clinical Interview Schedule – Revised (CIS-R).
P values were obtained from chi-square or analysis of variance test.
All *P* value <.01.

with 1 or more mood/anxiety diagnoses increased progressively as the frequency of migraine headaches augment. (Table 1).

In the multivariate logistic regression analyses, adjusted by age, gender, race, educational level, marital status, and family income, the associations between migraine and MDD, GAD, OCD, MADD, or CMD remained statistically significant. OR point estimates were, in general, higher with increasing migraine frequency (Table 2), and for MDD, GAD, and CMD, OR point estimates for daily migraine were the highest.

We also reviewed and present here data according to gender. For women (Table 3), with the exception for panic disorder, all other investigated psychiatric conditions were associated with the majority of migraine frequency strata. After Bonferroni correction for multiple comparisons, GAD and CMD (all strata), MDD (all but <1/month stratum), and OCD and MADD (1/month to 1/week and 2-6 days/week strata) remained statistically associated to migraine. For men (Table 4), logistic regression results also showed significant associations between migraine and all investigated psychiatric disorders except for panic disorder, which could not be calculated due to the small number of affected men. Probably because of the small number of men with migraine and psychiatric disorders in our study, most associations were not statistically significant after a Bonferroni correction. Only CMD (all strata but daily), OCD (daily), and MADD (<1/month) remained statistically associated with migraine. Gender interaction analysis revealed non-significant *P* values for interaction terms. Despite the higher OR in men compared with women, based on the results of interaction analysis, our data do not support the conclusion that OR in men are significantly higher than those found for women.

Table 2.—ORs (95% CI) for Mood Disorders and Anxiety According Migraine Frequency in 11,792 Participants From the ELSA-Brasil

	Migraine Frequency, OR (95% CI)				
Mood Disorders and Anxiety	No Migraine N = 10,531	<1×/Month N = 291	1×/Month-1×/Week N = 573	2-6×/Week N = 298	Daily N = 99
Major depressive disorder					
Crude OR	Reference (1.0)	3.08 (1.94-4.89)	3.38 (2.43-4.69)	5.97 (4.17-8.55)	12.69 (7.88-20.42)
Adjusted OR	Reference (1.0)	2.14 (1.33-3.43)	2.42 (1.71-3.42)*	3.82 (2.61-5.57)*	6.94 (4.20-11.49)*
Generalized anxiety disorder					
Crude OR	Reference (1.0)	3.00 (2.27-3.97)	2.92 (2.38-3.59)	4.40 (3.41-5.68)	6.99 (4.65-10.49)
Adjusted OR	Reference (1.0)	2.23 (1.67-2.98)*	2.20 (1.77-2.74)*	3.04 (2.32-3.97)*	4.04 (2.64-6.19)*
Panic disorder					
Crude OR	Reference (1.0)	3.12 (1.43-6.80)	1.34 (0.58-3.07)	1.72 (0.63-4.71)	3.98 (1.24-12.81)
Adjusted OR	Reference (1.0)	2.62 (1.17-5.87)	1.41 (0.59-3.36)	1.51 (0.53-4.26)	2.08 (0.61-7.06)
Obsessive-compulsive disorder					
Crude OR	Reference (1.0)	3.19 (1.75-5.82)	4.40 (2.97-6.53)	6.52 (4.16-10.22)	7.50 (3.70-15.19)
Adjusted OR	Reference (1.0)	2.44 (1.32-4.53)	3.52 (2.30-5.37)*	4.57 (2.82-7.43)*	4.16 (1.97-8.78)*
Mixed anxiety-depressive disorder					
Crude OR	Reference (1.0)	2.03 (1.50-2.75)	2.27 (1.83-2.80)	3.06 (2.34-3.99)	2.55 (1.58-4.11)
Adjusted OR	Reference (1.0)	1.65 (1.22-2.25)	1.83 (1.46-2.29)*	2.43 (1.84-3.21)*	1.86 (1.14-3.03)
Common mental disorder					
Crude OR	Reference (1.0)	3.39 (2.68-4.29)	3.66 (3.08-4.34)	6.97 (5.48-8.85)	14.69 (9.12-23.66)
Adjusted OR	Reference (1.0)	2.52 (1.97-3.22)*	2.75 (2.29-3.29)*	4.89 (3.81-6.28)*	8.80 (5.36-14.45)*

*These results persist significant after adjustment for multiple comparisons, $P < .0001$ except for daily frequency in OCD with a $P = .01$.

All multivariate analyses were adjusted for age, gender, race, educational level, marital status, family income, and Selective serotonin uptake inhibitor.

CI = confidence interval; OR = odds ratio; ELSA-Brasil = Brazilian Longitudinal Study of Adult Health.

Table 3.—ORs (95% CI) for Mood Disorders and Anxiety According Migraine Frequency in 5864 Female Participants From the ELSA-Brasil

	Migraine Frequency, OR (95% CI)				
Mood Disorders and Anxiety	No Migraine N = 4762	<1×/Month N = 242	1×/Month-1×/Week N = 505	2-6×/Week N = 263	Daily N = 92
Major depressive disorder					
Crude OR	Reference (1.0)	2.53 (1.56-4.09)	2.41 (1.68-3.45)	4.59 (3.14-6.72)	8.81 (5.32-14.58)
Adjusted OR	Reference (1.0)	2.24 (1.37-3.66)	2.23 (1.54-3.23)*	3.81 (2.57-5.65)*	6.42 (3.80-10.86)*
Generalized anxiety disorder					
Crude OR	Reference (1.0)	2.47 (1.82-3.35)	2.27 (1.81-2.84)	3.57 (2.72-4.70)	5.52 (3.61-8.43)
Adjusted OR	Reference (1.0)	2.21 (1.62-3.03)*	2.12 (1.68-2.68)*	3.03 (2.28-4.02)*	4.01 (2.58-6.24)*
Panic disorder					
Crude OR	Reference (1.0)	3.02 (1.27-7.19)	1.42 (0.60-3.37)	1.36 (0.42-4.44)	4.05 (1.23-13.30)
Adjusted OR	Reference (1.0)	2.68 (1.11-6.51)	1.64 (0.67-4.00)	1.33 (0.40-4.42)	2.28 (0.66-7.86)
Obsessive-compulsive disorder					
Crude OR	Reference (1.0)	2.62 (1.34-5.13)	3.59 (2.30-5.58)	5.85 (3.61-9.49)	5.07 (2.27-11.31)
Adjusted OR	Reference (1.0)	2.25 (1.14-4.43)	3.24 (2.05-5.13)*	4.70 (2.83-7.81)*	3.20 (1.39-7.38)
Mixed anxiety-depressive disorder					
Crude OR	Reference (1.0)	1.51 (1.07-2.13)	1.89 (1.50-2.38)	2.50 (1.88-3.34)	2.00 (1.21-3.30)
Adjusted OR	Reference (1.0)	1.41 (0.99-1.99)	1.78 (1.40-2.26)*	2.37 (1.76-3.19)*	1.74 (1.04-2.90)*
Common mental disorder					
Crude OR	Reference (1.0)	2.63 (2.03-3.42)	2.91 (2.41-3.50)	5.77 (4.45-7.50)	11.37 (6.90-18.75)
Adjusted OR	Reference (1.0)	2.34 (1.79-3.07)*	2.70 (2.22-3.28)*	5.02 (3.83-6.57)*	8.64 (5.14-14.51)*

*These results persist significant after adjustment for multiple comparisons, $P < .0001$.
All multivariate analyses were adjusted for age, race, educational level, marital status, family income, and selective serotonin uptake inhibitor.
CI = confidence interval; OR = odds ratio; ELSA-Brasil = Brazilian Longitudinal Study of Adult Health.

Finally, analyzing probable migraine together with definite migraine cases, or restricting the reference group to individuals without any headache did not significantly change the results.

DISCUSSION

Our findings revealed that mood/anxiety disorders were positively associated to migraine diagnosis in both genders, except for panic disorder. One or more psychiatric comorbidities were almost 5 times more frequent among daily migraineurs compared with individuals with non-migraine headaches. In most comparisons, ORs for investigated psychiatric disorders were progressively higher as migraine frequency increased suggesting a likely "dose-response" effect for both genders. The inclusion of probable and definite cases of migraine together in the analysis did not change the results, but there was a decrease in the magnitude of association.

Despite the higher frequencies of migraine and mood/anxiety disorders among women compared with men, we found that men presented with numerically higher ORs of having CMDs and OCD only for daily frequency. Although the results of the interaction regression models do not allow us to state this with certainty, it might be possible that psychiatric disorders could have a more important effect on men compared with women, who have other gender-specific factors associated to migraine as hormones during menstrual cycle. This highlights the role of psychiatric disorders in migraine among men.

Overall, previous studies that examined the relationship between migraine frequency and mood/anxiety disorders; related ORs ranged from 2 to 3 among those individuals who had higher frequencies of migraine episodes.[16-18] However, most of these analyses did not perform separate analyses for men and women.[3,6,16,17] Beyond that, they used

Table 4.—ORs (95% CI) for Mood Disorders and Anxiety According Migraine Frequency in 5928 Male Participants From the ELSA-Brasil

	Migraine Frequency, OR (95% CI)				
Mood Disorders and Anxiety	No Migraine N = 5769	<1×/Month N = 49	1×/Month-1×/Week N = 68	2-6×/Week N = 35	Daily N = 7
Major depressive disorder					
Crude OR	Reference (1.0)	1.24 (0.17-9.11)	4.74 (1.86-12.05)	3.62 (0.85-15.30)	23.88 (4.57-124.62)
Adjusted OR	Reference (1.0)	1.19 (0.16-8.87)	4.87 (1.86-12.73)	3.22 (0.74-14.07)	19.30 (2.94-126.61)
Generalized anxiety disorder					
Crude OR	Reference (1.0)	2.53 (1.18-5.43)	3.24 (1.75-5.99)	3.24 (1.41-7.46)	5.18 (1.00-26.79)
Adjusted OR	Reference (1.0)	2.29 (1.05-4.97)	2.98 (1.56-5.69)	3.03 (1.29-7.13)	3.63 (0.66-20.09)
Panic disorder					
Crude OR	Reference (1.0)	—	—	—	—
Adjusted OR	Reference (1.0)	—	—	—	—
Obsessive-compulsive disorder					
Crude OR	Reference (1.0)	3.85 (0.92-16.20)	5.66 (2.00-16.01)	2.66 (0.36-19.75)	36.20 (6.89-190.13)
Adjusted OR	Reference (1.0)	3.29 (0.77-14.10)	5.57 (1.93-16.08)	2.33 (0.31-17.63)	29.86 (4.66-191.43)*
Mixed anxiety-depressive disorder					
Crude OR	Reference (1.0)	3.58 (1.86-6.91)	2.13 (1.11-4.09)	3.27 (1.48-7.24)	4.42 (0.85-22.83)
Adjusted OR	Reference (1.0)	3.25 (1.67-6.35)*	2.17 (1.12-4.20)	2.68 (1.15-6.26)	3.96 (0.75-20.96)
Common mental disorder					
Crude OR	Reference (1.0)	3.82 (2.15-6.78)	3.22 (1.96-5.30)	4.67 (2.39-9.11)	13.98 (2.70-72.46)
Adjusted OR	Reference (1.0)	3.43 (1.91-6.18)*	3.13 (1.87-5.25)*	4.08 (2.02-8.21)*	10.70 (2.03-56.32)

*These results persist significant after adjustment for multiple comparisons, $P < .05$.
All multivariate analyses were adjusted for age, gender, race, educational level, marital status, family income, and selective serotonin uptake inhibitor.
— = not applicable; CI = confidence interval; OR = odds ratio; ELSA-Brasil = Brazilian Longitudinal Study of Adult Health.

screening questionnaires for assessing psychiatric comorbidities.[3,16,17]

In the American Migraine Prevalence and Prevention (AMPP) Study, a population-based survey, depression was measured both by self-reported of physician diagnosis of depression and by using the Patient Health Questionnaire (PHQ-9).[17] According to their findings, individuals with chronic migraine (≥15 days of headache per month) had a 2-fold risk of having depression or anxiety compared with episodic (0-14 days of episodes per month) cases.[17] In a web-based survey performed by Blumenfeld et al, chronic migraine was compared with episodic migraine, and their results were similar for the association between migraine frequency and depression/anxiety, assessed by PHQ-4 items.[16]

In fact, our results are also consistent with the Nord–Trondelag Health Study (HUNT-2), in which a noticeable increase in the ORs for the association between migraine frequency and depression/anxiety disorders using individuals with no headache as a reference group was observed.[18] However, the assessment of anxiety and depression was performed by the Hospital Anxiety and Depression Scale (HADS). In comparison with no headache individuals, the odds (adjusted by age, sex and education) of depression in migraine sufferers occurring on 7 or fewer days per month was 2.0 (95% confidence interval [CI] 1.6-2.5), 7-14 days per month was 4.2 (95% CI 3.2-5.6), and more than 15 days per month was 6.4 (95% CI 4.4-9.3). Similar results were also described for anxiety disorders. Although the study consisted of 28% of male in the migraine headache subgroup, they did not perform any stratified analysis by gender.[18]

There is scarce information in the literature about the association between OCD and migraine headaches. Most articles discussed a specific aspect related to the difficulties of treating chronic migraine

when it is associated with OCD.[19,20] The Spectrum project studied 50 patients with chronic migraine (80% women) and found a frequency of 28% of OCD as a trait using a questionnaire developed for the project. No information about frequency of OCD for gender was available.[19] Another study evaluated psychiatric comorbidity in 158 patients with migraine. A frequency of OCD of 2.3% in patients with migraine was found. Once again, no information was included regarding gender.[20]

In Brazil, data regarding the relationship between migraine and mood/anxiety disorders is scarce.[21-23] One did evaluate the association of headache and psychiatric disorders in a population sample in the city of São Paulo and classified the study participants according to their psychiatric condition using The World Health Organization Composite International Diagnostic Interview.[24] However, the questionnaire used did not classify migraine according to IHS criteria. The OR for headache among participants with "nervousness, tension, or mental illness" was elevated for depressive episodes (OR 2.1; 95% CI 1.4-3.4), dysthymia (OR 3.4; 95% CI 1.6-7.4), and generalized anxiety disorder (OR 4.3; 95% CI 2.1-8.6) when compared with patients without headache.

Because of the low frequency of panic disorder in our cohort (less than 1.2% including individuals with probable migraine), we could not find any statistically significant association with migraine frequency. A National Population-based Study from the Canadian Community Health Survey including 36,984 individuals has demonstrated that presence of panic disorders at baseline is associated to transformation of episodic to chronic migraine.[6] In another longitudinal study, migraine and other severe headaches were associated with an increased risk for first onset of panic disorder, and panic disorder was associated with an increased risk for first onset of migraine and for first onset of other severe headaches.[25]

This is a cross-sectional analysis, and panic was associated with the lowest and the highest migraine frequency in women but not with the middle frequencies. The small frequency of panic disorder in men did not permit the analysis in male participants. Thus, we cannot rule out a type II error reaching our sample even for women.

Our most compelling point from our analyses lies in the consistent and strong association between migraine headaches and psychiatric comorbidities. The strength of the association tends to increase as the frequency of migraine increases, suggesting a likely "dose-response" effect between migraine headache and mood/anxiety disorders, particularly MDD, GAD, and CMD for women and CMDs for men. To the best of our knowledge, the association between migraine frequency and OCD was not previously described by other studies in men and women. However, this association was restricted to some frequency in women and daily frequency in men.

Our study has some strengths. Brazilian prevalence of migraine headaches[12,26] and of psychiatric disorders, especially in metropolitan areas, is high[27,28] creating a good setting to perform these analyses. Migraine and psychiatric diagnoses were assessed on face-to-face interviews performed by trained professionals using well-known instruments in the ELSA-Brasil. For instance, the CIS-R is a very reliable and standardized tool for diagnosing mood and anxiety disorders, which can be used in large scale, requiring little or no judgment by interviewer in a quite short time of administration.[15] Our data are derived from a large sample including a good proportion of men. Of note, 12.6% (159/1261) of the migraine headaches diagnosed in our study were reported by males, permitting additional analyses with mood/anxiety disorders and migraine frequency stratified by gender. However, even with a higher frequency of men in the sample, for most categories of psychiatric disorders, our study does not have sufficient power to show an association with migraine frequency.

Our data also have some limitations. Despite strong associations between migraine headaches and mood/anxiety disorders because of being a cross-sectional analysis, we cannot make any causal inferences. However, one important limitation of the study is the impossibility of classifying headache as episodic or chronic as we did not have information on whether participants presented with more than 15 days of pain per month. Nevertheless, we still could suggest for most comparisons a likely "dose-response" effect; as frequency of migraine headache increased, the strength of the association has also increased for

almost all psychiatric disorders for total sample, for MDD, GAD, OCD, and CMDs for women and CMDs for men.

In conclusion, this is a cross-sectional analysis performed in a large multicentric Brazilian study, demonstrating that an increase in the frequency of migraine episodes has a progressive and stronger association with mood/anxiety disorders. With men in particular, we found a strong and consistent association between daily migraine, and OCD and CMDs.

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