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Association of mental health symptoms with the migraine-tension-type headache spectrum in the Brazilian longitudinal study of adult health

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ABSTRACT

Objective: To investigate the relationship between mental health symptoms and the migraine-tension-type headache (TTH) spectrum in middle-aged adults from the Brazilian Longitudinal Study of Adult Health (ELSA-Brasil study).

Methods: In this cross-sectional analysis (baseline data: 2008–2010), it was evaluated the relationship between each mental health symptom assessed by the Clinical Interview Schedule-Revised (CIS-R) questionnaire and headache subtypes (migraine and TTH) according to international criteria. It was performed binary logistic regression models, with estimated odds ratios (OR) with their respective 95% confidence intervals (CI) adjusted for confounders including migraine attack frequency.

Results: Among 13,916 participants, 70.1% reported any major primary headache subtype within the last year. The most common subtype was definite TTH (33.4%), followed by probable migraine (21.0%), definite migraine (8.5%), and probable TTH (7.2%). Our main findings indicated positive associations between anxiety-related symptoms and the migraine-tension type headache (TTH) spectrum with a clear trend toward definite migraine more than tension-type headache. The presence of somatic symptoms presented a high likelihood for the associations with headaches, mainly definite migraine (OR: 7.9, 95% CI: 6.4–9.8), probable migraine (OR: 4.5, 95% CI 3.7–5.4) and probable TTH (OR: 3.0, 95% CI: 2.3–3.8). Other symptoms associated with headache disorders included fatigue, panic, irritability, anxiety symptoms, concentration problems, forgetfulness, depressive symptoms, and worry. The effect of associations remained significant after controlling for headache attack frequency.

Conclusion: This study provides evidence of consistent associations between mental health symptoms and primary headache disorders, with a higher burden of anxiety-based symptoms observed in people with migraine than those with TTH.

1. Introduction

Migraine and tension-type headache (TTH) can be considered as a continuum where a spectrum of aspects, such as pulsating quality, photophobia, phonophobia, nausea and vomiting, unilateral pain and severity, range from less (TTH) to more prominent features (migraine). The diagnostic criteria defined by the International Classification of Headache Disorders [1] include the spectrum from definite migraine, probable migraine, probable TTH, to definite TTH. Patients with migraine and TTH are at an increased risk of concurrent psychiatric disorders. Although a bi-directional relation has been established [2,3] little is known about the relationship between mental symptoms and migraine-TTH spectrum [4,5]. Anxiety and mood disorders have been shown to be the most relevant psychiatric comorbidities associated with

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migraine, with impact on its prevalence, prognosis, treatment, and clinical associated outcomes [6–9]. Moreover, anxiety and depressive symptoms can be present in a small but significant proportion of individuals with TTH, leading to an exacerbation of clinical symptoms of both clinical conditions [10]. Even if operational diagnostic criteria are not met, the co-occurrence of mental symptoms could be clinically relevant among individuals with primary headaches [11–13].

Previous literature has reported that vegetative symptoms of depression (loss of appetite, fatigue, poor sleep) are more likely associated with migraine than mood symptoms [11]. In addition, separate symptoms of anxiety have presented a much higher association with migraine than the categorical diagnosis of generalized anxiety disorder (GAD) [11,12]. In this context, the symptom-based approach might have clinical implications on prevention of chronification, as well as treatment refractoriness and loss of quality of life [14,15]. Since migraine is a multifactorial disorder, with genetic, hormonal, environmental, dietary, sleep, and psychological aspects playing a different role at the individual level [13,16], this symptom-based methodology can be useful to uncover the role of mental symptoms in patients with primary headache [17].

Findings from the Brazilian Longitudinal Study of Adult Health (ELSA-Brasil), a large ongoing multicentric cohort study performed in middle-aged individuals in Latin America, have indicated a noticeable association between migraine and psychiatric disorders, based on the Clinical Interview Schedule – Revised (CIS-R) [18,19]. However, no analyses have investigated the association between psychiatric diagnoses and TTH, nor with mental symptoms and primary headaches. [18] Thus, we aimed to evaluate the relationship between each mental symptom based on a face-to-face interview using CIS-R questionnaire and the migraine-TTH spectrum in the ELSA-Brasil study [19–21].

2. Methods

2.1. Study design and population

We cross-sectionally evaluated the baseline data (2008–2010) of participants from the ELSA-Brasil cohort. In brief, ELSA-Brasil is a multicentric study with 15,105 civil servants of both sexes aged 35–74 years at baseline. Participants were enrolled in five public universities and one research institution located in the Northeast, Southeast, and South regions of Brazil in six different states (Bahia, Espírito Santo, Minas Gerais, Rio Grande do Sul, São Paulo and Rio de Janeiro) [19–21]. Both active and retired employees were eligible for the study. The baseline assessment was conducted between August 2008 and December 2010 and consisted of a 7-h examination and face-to-face interviews including mental health and headache symptoms evaluation [19–21].

Exclusion criteria were current or recent pregnancy (< 4 months before the first interview), intention to soon quit working at the institution, severe cognitive or communication impairment, and if retired, residing outside the metropolitan catchment area of the participant center.

Institutional review boards (CEP-HU/USP: #659/06) and the National Research Ethics Committee (CAAE: #08109612.7.1001.0076) approved this study on May 19, 2006, and all participants agreed and signed the informed consent. This study complies with the STROBE guidelines for reporting data from observational research.

2.2. Assessment tools

The psychopathological data were collected by trained lay interviewers using the Brazilian-Portuguese version of the Clinical Interview Schedule – Revised (CIS-R), which was adapted and validated in the ELSA-Brasil study [22,23]. There are reliability studies of the CIS-R conducted in various countries, languages and settings [24–27]. Validation studies have been conducted by comparing the CIS-R with other diagnostic tools, including structured interviews like the CIDI and SCID [26] and the SCAN [27]. These findings further support the robustness and applicability of the CIS-R across various clinical contexts and populations [25]. Assessing the validity of only evaluating symptoms is crucial. By focusing on symptom clusters, we can gain a more nuanced understanding of mental health disorders. Evaluating symptomatic clusters allows for a comprehensive insight into the severity, duration, and interrelation of symptoms, which might not be captured when solely focusing on broader diagnostic criteria.

This structured schedule assesses common mental disorders (CMD) from a bottom-up perspective. The complete CIS-R version includes 14 sections covering symptoms of CMD that are present in the last week at a level that causes distress and interference in daily activities. The symptoms are somatic complaints (pain, including headache), fatigue, concentration and forgetfulness, sleep disturbance, irritability, worry about physical health, depressive symptoms, depression ideas, worry, anxiety symptoms, phobias, panic attacks, compulsions, and obsessions. Each section begins with a number of mandatory filter questions that establish the existence of a particular symptom in the past month. The presence of a positive symptom leads to a more detailed assessment of the specific symptom to determine a score for each section. If any mental health symptom was present over the previous month, the interviewer was advised to ask about the specific symptom in the previous week (in terms of frequency, duration, severity, and time since onset) to determine a score for each section. Possible scores range from 0 to 4 on each section (except the section on depressive ideas, which has a maximum score of 5). Each symptom is considered clinically relevant if the score reaches two or more in the corresponding sections [23,28,29]. For example, in the CIS-R, the depressive symptoms (not a clinical diagnosis of depression) were explored with core questions examining sadness, depression, and diminished interest or pleasure in doing things for a period. The accessory symptoms of depressive ideas were investigated with questions about sexual drive; agitation or retardation; feeling worthless or excessive/inappropriate guilt; hopelessness, thoughts of death, and suicide [29]. Anxiety symptoms (not the full-blown diagnosis of anxiety) were investigated with inquiries examining feeling anxious or nervous, muscle tension, not being able to relax, shortness of breath, fast heartbeat, sweating, and dizziness [29]. Neither depressive nor anxiety symptoms were linked to a clinical definition in our study. We did not evaluate the full-blown diagnosis because we aimed to evaluate the symptom-based association with migraine subtypes.

2.3. Primary headaches

All participants in the study ($N = 15{,}105$) 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 Classification of Headache Disorders – ICHD, 2nd Edition, which was validated and previously used in Brazil [30]. Briefly, it investigates pain frequency, duration, quality, location, intensity, triggering factors, and accompanying symptoms, such as nausea or vomiting. Participants fulfilling all criteria for migraine and TTH were classified accordingly. If participants fulfilled all criteria but one for migraine or TTH, they were classified as probable migraine or probable TTH, respectively. The data on headache attack frequency was collected through closed-ended questions with the following response options: “once in a while”, “1 to 2 per month”, “once a week”, “more than once a week”, and “daily”.

2.4. Demographic and clinical variables

We assessed sociodemographic variables such as sex, age, marital status (married, separated, single, widowed and other), monthly household income (< US$1245, US$1245-3319, and > US$3319), educational level (elementary, high school, or college) and self-identified skin colour (White, Black, Brown or Pardo, Other – Indigenous, Asian). The skin colour or race of the Brazilian population is based

on participants' self-identification, according to the Brazilian Population Census Survey 2022. There are five options: White, Black, Brown ("Pardo"), Indigenous, and Yellow, which in this latter case refers to people of Asian descent, such as Japanese, Chinese or Korean. Black people are descended from Africans and White people from Europeans. Pardo Brazilians are individuals of interracial ancestry from these ethnic groups. This methodology is dominant in Brazilian studies as it takes account of historical and theoretical context [31].

Lifestyle variables were smoking status (never, former, current), leisure-time and commuting physical activity (PA) levels (continuous values) according to the International Physical Activity Questionnaire (IPAQ) long form [32].

We determined cardiometabolic variables using standardized methods for measuring body mass index (BMI), blood pressure, fasting glycemia, total cholesterol, LDL and HDL cholesterol, and triglycerides (glycated hemoglobin (HbA1C). Hypertension was diagnosed if the subject had a history of hypertension and/or systolic blood pressure was $\geq$140 mmHg and/or diastolic blood pressure was $\geq$90 mmHg, or if they were taking medication for hypertension. Diabetes was diagnosed if the subject had a history of diabetes, a fasting plasma glucose $\geq$126 mg/dl, a two-hour plasma glucose $\geq$200 mg/dl, or an HbA1C $\geq$ 6.5%. Dyslipidaemia, metabolic syndrome [33] and obesity (BMI $\geq$ 30 Kg/m^2) [34] were defined according to established criteria.

Details of prophylactic medications for migraine based on the American Academy of Neurology guidelines were also collected as follows: Level A: Divalproex sodium, sodium valproate, topiramate, propranolol, metoprolol and timolol; Level B: Amitriptyline, venlafaxine, atenolol and nadolol [35].

2.5. Statistical analysis

Descriptive data were calculated as absolute numbers with respective frequencies for categorical variables. Continuous variables are reported as mean with standard deviation (SD±) by the distribution of each variable attested by the Kolmogorov-Smirnov normality test. Chi-Square and one-way ANOVA tests were used to compare sociodemographic and lifestyle variables, previous comorbidities and mental health symptoms according to headaches subgroups (no headache, definite and probable migrane and TTH).

In this study, any missing data in the selected variables mentioned above were removed from the analysis. This approach was deemed acceptable and did not pose a problem, mainly due to the large sample size of the ELSA-Brasil study, where around 92% of participants still had complete data for all the variables examined.

From binary logistic regression models, we computed the odds ratios (OR) with their respective 95% confidence intervals (95% CI) for the relationship between each mental health symptom (yes/no, the later set as reference) entered as the dependent variable and the primary headache subtypes as independent variables ("no headache" was set as the reference). We performed age- and sex-adjusted models (Model 1) and fully adjusted models (Model 2). In the fully adjusted models, we controlled for the effects of sex, age (continuous), BMI (continuous), leisure-time and commuting physical activity levels (continuous), smoking status (never, former, current), monthly household income ($<$ US$1245; US$1245-3319; and $>$ US$3319), educational level (elementary, high school, or college), self-identified skin colour (White, Black, Brown (Pardo), Other – Indigenous, Asian), and marital status (married, separated, single, widowed and other), prophylactic medication (yes/no), hypertension (yes/no), diabetes (yes/no), metabolic syndrome (yes/no), and dyslipidemia (yes/no). All models were performed in total sample and stratified by sex. In addition, we investigated whether sex was a modifier of the association between headaches` subtypes to each mental health symptom by adding a two-way interaction term among each headache diagnosis * sex with mental health symptom as outcome in fully adjusted binary regression models. In the models that included interaction term, the reference category for sex was 'male' due to their lower frequency of headaches compared to female. The same confounder variables were included in the final models.

Finally, to investigate whether headache attack frequency could impact potential associations between headache disorders and mental health symptoms, we conducted a sensitivity analysis including the frequency of attacks (n = 9757) in the adjusted models. Definite TTH was selected as the reference group in this analysis since it was the most prevalent headache type with the lowest attack frequency. The frequency of headache attacks was presented as a categorical variable. Finally, we further explored the associations between frequency of attacks and somatic symptoms. In the fully adjusted model, we also controlled for headache subtypes.

For all analyses, p-values $<$0.05 were also considered statistically significant. We used Statistical Package for the Social Sciences (SPSS) software (IBM SPSS Statistics for Windows, Version 24.0. IBM Corp., Armonk, NY, USA) to compute the statistics.

3. Results

Of 15,105 participants in the ELSA-Brasil, we first excluded baseline data from participants with other headaches not migraine neither TTH (n = 139), missing information about headaches (n = 13), missing information on mental health symptoms (n = 342), and missing information in any of the other variables: sociodemographic (sex, age, race, educational level, marital status, monthly household income), lifestyle (physical activity and smoking) and comorbidities (hypertension, diabetes, dyslipidemia, metabolic syndrome), and prophylactic medication for migraine (n = 695). In the end, we evaluated data from 13,916 participants (mean age: 52.1 years (SD ± 9.08), 54.3% female) who had complete data about primary headaches and mental health symptoms (somatic complaints (pain, including headache), fatigue, concentration and forgetfulness, sleep disturbance, irritability, worry about physical health, depressive symptoms (not a clinical diagnosis of depression), depression ideas, worry, anxiety symptoms (not a clinical diagnosis of anxiety), phobias, panic attacks, compulsions, and obsessions. (Supplemental Fig. 1).

Overall, 70.1% reported any major primary headache subtype within the last year. The most common subtype was definite TTH (33.4%), followed by probable migraine (21.0%), definite migraine (8.5%), and probable TTH (7.2%). The main baseline sociodemographic characteristics of participants are described in Table 1. Overall, the sample presented a heterogeneous sociodemographic characteristic, with participants with definite migraine being mostly female, younger, black, with secondary education, lower income, and lower physical activity levels than other subgroups. Also, among those with definite migraine, it was verified a higher headache attack frequency compared to other headache groups. Meanwhile participants with any primary headache presented lower frequency of metabolic comorbidities than participants without headache disorders (Table 1).

The frequency of mental symptoms according to primary headache subtype for all sample by sex is shown in Table 2. All groups of primary headache disorders presented a higher frequency of mental symptoms when compared with those with no headaches, regardless of sex. Overall, it was observed higher frequencies (about 50% or more) of mental health symptoms afflicting more individuals with migraine than TTH. Fatigue, worry and sleep problems were the most often mental symptoms reported by participants with these major headache disorders. Particularly among those with definite migraine, the top three main mental health symptoms reported were fatigue (60.9%), worry (58.7%) and sleep problems (48.9%). Among those with probable migraine, worry and fatigue were the most frequent symptoms (50.3% and 49.8%, respectively). Among individuals with TTH (definite and probable), worry was also the most common mental health symptom reported by 39.4% and 44.7% of participants, respectively.

After considering full adjustments in the regression models performed in all sample and stratified by sex, a similar pattern of

Table 1
Baseline characteristics of 13,916 participants according to major primary headaches subtype in the ELSA-Brasil study.

	No headaches	Definite migraine	Probable migraine	Definite TTH	Probable TTH
	(*n* = 4159)	(*n* = 1181)	(*n* = 2920)	(n = 4651)	(*n* = 1005)
Age, years, Median (IQR)	56.0 (48.0–62.0)	48.0 (43.0–54.0)[*,#, †, ‡]	49.0 (44.0–56.0)[#, †, ‡]	50.0 (44.0–57.0)[†, ‡]	51.0 (45.0–57.0) [‡]
Female	1586 (38.1)	1036 (87.7) [a,b,c,d]	2091 (71.6) [b,c,d]	2266 (48.7) [c,d]	582 (57.9) [d]
Male	2573 (61.9)	145 (12.3) [a,b,c,d]	829 (28.4) [b,c,d]	2385 (51.3) [c,d]	423 (42.1) [d]
Race (self-identified skin colour), n (%)					
White	2075 (49.9)	582(49.3) [b]	1478 (50.6) [b]	2558(55.0)	523(52.0)
Brown ("Pardo")	1208 (29.0)	326(27.6)	861(29.4) [b]	1257(27.0)	294 (29.3)
Black	711 (17.1)	231(19.6) [a,b,c,d]	486(16.6) [b]	681(14.6) [d]	151(15.0)
Other (Asian, Indigenous)	165(4.0)	42(3.6)	95(3.3)	155(3.3)	37(3.7)
Education, n (%)					
Elementary	726 (17.5)	116(9.8) [c,d]	331(11.3) [d]	491(10.6) [d]	134 (13.4) [d]
High School	1399 (33.6)	496(42.0) [a,b,c,d]	1128(38.6) [b,c,d]	1455 (31.2) [d]	342 (34.1)
College	2034 (48.9)	569(48.2) [b,c]	1461 (50.1) [b]	2705 (58.2)	529 (52.5)
Monthly Household Income, US$, n (%),					
≤ USD 1245	1193 (28.7)	371 (31.4) [a,b,c]	826 (28.3) [b]	1063 (22.9) [d]	257 (25.6)
USD 1245–3319	1699 (40.8)	558 (47.2) [b,d]	1375 (47.1) [b,d]	2002 (43.0) [c,d]	473 (47.1) [d]
≥ USD 3319	1267 (30.5)	252 (21.3) [a,b,c,d]	719 (24.6) [b,d]	1586 (34.1) [c,d]	275 (27.4) [d]
Marital Status, n (%)					
Married	2810 (67.6)	695 (58.8) [a,b,c,d]	1897 (65.0) [b,d]	3182 (68.4) [c]	642 (63.9) [d]
Separated	638 (15.3)	221 (18.7) [b,d]	515 (17.6) [b,d]	707 (15.2)	178 (17.7)
Single	402 (9.7)	167 (14.1) [a,b,c,d]	268 (9.2)	447 (9.6)	112 (11.1)
Widowed	192 (4.6)	51 (4.3)	136 (4.7) [b]	159 (3.4) [d]	38 (3.8)
Other	117 (2.8)	47 (4.0) [d]	104 (3.6)	156 (3.4)	35 (3.5)
Migraine Prophylactic Medication, yes, n (%)	206(4.9)	133(11.2) [b,c,d]	273(9.3) [b,c,d]	289(6.2) [d]	62(6.1)
Headache Attacks' Frequency, n (%)					
Once in a while	–	266 (22.5) [a,b,c]	1277 (43.7) [b,c]	3119 (67.1) [c]	620 (61.7)
1–2 times/month	–	397 (33.6) [a,b,c]	767 (26.3) [b,c]	859 (18.5)	183 (18.2)
Once a week	–	141 (11.9) [b]	298 (10.2) [b]	295 (6.3)	92 (9.2) [b]
More than once a week	–	283 (24.0) [b]	452 (15.5) [b]	306 (6.6)	85 (8.5) [b]
Daily	–	94 (8.0) [a,b,c]	126 (4.3) [b,c]	72 (1.5)	25 (2.5)
BMI, kg/m^2), Median (IQR)	26.7 (23.8–29.7)	26.1 (23.4–29.4)	26.4 (23.4–29.8)	26.2 (23.6–29.3) [‡]	26.4 (23.7–29.4)
Smoking, n (%)					
Current	585 (14.1)	161 (13.6)	374 (12.8)	554 (11.9) [d]	129 (12.8)
Former	1405 (33.8)	291 (24.6) [a,b,c,d]	813 (27.8) [d]	1386 (29.8) [d]	290 (28.9) [d]
Never	2169 (52.1)	729 (61.8) [b,d]	1,73 3(59.4) [d]	2711 (58.3) [d]	586 (58.3) [d]
Hypertension, n (%)	1827 (43.9)	313 (26.5) [a,b,c,d]	937 (32.1) [d]	1576 (33.9) [d]	350 (34.8) [d]
Diabetes, n (%)	1095 (26.3)	167 (14.1) [b,d]	483 (16.5) [d]	819 (17.6) [d]	179 (17.8) [d]
Metabolic Syndrome, n (%)	544 (13.1)	150 (12.7)	350 (12.0)	480 (10.3) [d]	115 (11.4)
Dyslipidaemia, n (%)	2791 (67.2)	799 (61.7) [d]	1768 (63.1) [d]	2936 (63.2) [d]	607 (60.5) [d]
LTPA, min/week, Mean (±SD)	156.6 (210.0)	101.2 (171.8) [#, †, ‡]	113.2(163.7) [#, ‡]	140.5(193.8) [‡]	127.4(172.3) [‡]
CPA, min./week, Mean (±SD)	181.1 (296.2)	145.9 (209.1) [‡]	153.1 (243.3) [‡]	154.4(265.8) [‡]	152.6(276.4) [‡]

TTH: Tension-Type Headache; CIS-R: Clinical Interview Schedule – Revised (CIS-R). LTPA: Leisure-time Physical Activity; CPA: Commuting Physical Activity; ELSA-Brasil: Brazilian Longitudinal Study of Adult Health; BMI: Body mass index.

[*] *p*-value <0.05 *vs* Probable Migraine.
[#] p-value <0.05 *vs* Definite TTH.
[†] p-value <0.05 *vs* Probable TTH.
[‡] p-value <0.05 *vs* No Headache, One-Way ANOVA, Bonferroni-adjusted pairwise comparisons.
[a] *p*-value <0.05 *vs* Probable Migraine.
[b] *p*-value <0.05 *vs* Definite TTH.
[c] p-value <0.05 *vs* Probable TTH.
[d] p-value <0.05 *vs* No Headache, Bonferroni-corrected Chi-Square tests.

association was observed, which revealed the highest ORs for the relationship between somatic symptoms and major primary headaches, mainly definite migraine (Supplemental Tables 1–3). In the total sample, participants with definite migraine presented the highest likelihood of somatic complaints (OR: 7.9, 95% CI: 6.4–9.8), followed by probable migraine (OR: 4.5, 95% CI:3.7–5.4), probable TTH (OR: 3.0, 95% CI: 2.3–3.8), and definite TTH (OR: 1.7, 95% CI: 1.4–2.1). Symptoms of fatigue were also consistently associated with major primary headache disorders, as follows: definite migraine (OR: 5.4, 95% CI: 4.7–6.3), probable migraine (OR: 3.6, 95% CI: 3.2–4.0), probable TTH (OR: 2.5, 95% CI: 2.1–2.9), and definite TTH (OR: 1.5, 95% CI: 1.4–1.7). Additional mental symptoms associated with headache disorders were panic, irritability, anxiety symptoms, concentration problems, and forgetfulness.

Considering sexes differences, worry (59.2%) and fatigue (64.2%) were the most frequent symptoms observed in the subgroup of females with definite migraine, as well as among males with definite migraine the main complaint reported was worry (55.2%). In the fully regressions models, both sexes presented the highest adjusted ORs for the association between definite migraine and somatic symptoms (females: OR: 5.8; 95% CI: 4.5–7.6 and males: OR: 7.9; 95% CI: 4.9–12.7) (Supplemental Tables 2 and 3). Also, male presented more mental complaints related to a definite migraine diagnosis than female. Among female, progressively higher ORs (ranging between 2.8 and 5.8) were observed for the associations between definite migraine, somatic symptoms, fatigue, panic, and irritability compared to the no headaches subgroup (Supplemental Table 2). In males, compared to the no headache subgroup, the adjusted models also showed higher ORs (ranging between 3.1 and 7.9) for the associations between definite migraine and the following mental health symptoms: somatic symptoms, panic, irritability, concentration and forgetfulness, phobias, compulsions, fatigue, depressive symptoms, worry and anxiety symptoms. (Supplemental Table 3). Regarding sleep problems, we still observed a positive relationship between sleep complaints and headaches in the multivariate logistic regression models

Table 2
Mental health symptoms of 13,916 participants according to major primary headaches subtype in the baseline of ELSA-Brasil study.

Total symptoms (CIS-R), n (%)	No headaches (n = 4159)	Definite migraine (n = 1181)	Probable migraine (n = 2920)	Definite TTH (n = 4651)	Probable TTH (n = 1005)
Somatic Symptoms	172 (4.1)	327 (27.7) [a,b,c,d]	507 (17.4) [b,c,d]	321 (6.9) [c,d]	118 (11.7) [d]
Fatigue	791 (19.0)	719 (60.9) [a,b,c,d]	1454 (49.8) [b,c,d]	1340 (28.8) [c,d]	395 (39.2) [d]
Concentration and Forgetfulness	395 (9.5)	382 (32.4) [a,b,c,d]	689 (23.6) [b,c,d]	520 (11.2) [c]	191 (18.9) [d]
Sleep Problems	1037 (24.9)	577 (48.9) [a,b,c,d]	1274 (43.6) [b,c,d]	1443 (31.0) [c,d]	384 (38.1) [d]
Irritability	647 (15.6)	489 (41.3) [a,b,c,d]	977 (33.4) [b,c,d]	915 (19.7) [c,d]	277 (27.5) [d]
Worry About Physical Health	457 (11.0)	247 (20.9) [b,c,d]	564 (19.3) [b,c,d]	506 (10.9) [c]	148 (14.7) [d]
Depressive Symptoms	394 (9.5)	306 (25.9) [a,b,c,d]	555 (19.0) [b,c,d]	455 (9.8) [c]	135 (13.4) [d]
Depressive Ideas	313 (7.5)	268 (22.7) [b,c,d]	568 (19.4) [b,c,d]	395 (8.5) [c]	130 (12.9) [d]
Worry	1269 (30.5)	693 (58.7) [a,b,c,d]	1470 (50.3) [b,c,d]	1834 (39.4) [c,d]	449 (44.7) [d]
Anxiety Symptoms	662 (15.9)	514 (43.5) [a,b,c,d]	1076 (36.8) [b,c,d]	957 (20.6) [c,d]	294 (29.2) [d]
Phobias	201 (4.8)	187 (15.8) [a,b,c,d]	353 (12.1) [b,c,d]	267 (5.7)	75 (7.4) [d]
Panic	78 (1.9)	90 (7.6) [a,b,d]	171 (5.8) [b,d]	101 (2.2) [c]	50 (5.0) [d]
Compulsions	294 (7.1)	202 (17.1) [b,c,d]	403 (13.8) [b,d]	325 (7.0)	126 (12.5) [d]
Obsessions	429 (10.3)	253 (21.4) [a,b,c,d]	507 (17.3) [b,c,d]	529 (11.4)	129 (12.8)
Female (n = 7561)	No headaches (n = 1586)	Definite migraine (n = 1036)	Probable migraine (n = 2091)	Definite TTH (n = 2266)	Probable TTH (n = 582)
Somatic Symptoms	94 (5.9)	296 (28.6) [a,b,c,d]	402 (19.2) [b,c,d]	213 (9.4) [c,d]	75 (12.9) [d]
Fatigue	440 (27.7)	665 (64.2) [a,b,c,d]	1160 (55.5) [b,c,d]	850 (37.5) [c,d]	281 (48.3) [d]
Concentration and Forgetfulness	215 (13.6)	348 (33.6) [a,b,c,d]	535 (25.6) [b,c,d]	332 (14.6) [c]	125 (21.4) [d]
Sleep Problems	443 (27.9)	522 (50.4) [a,b,c,d]	931 (44.5) [b,c,d]	761 (33.6) [c,d]	225 (38.6) [d]
Irritability	271 (17.1)	427 (41.1) [a,b,c,d]	725 (34.7) [b,c,d]	491 (21.6) [c,d]	173 (29.7) [d]
Worry About Physical Health	205 (12.9)	222 (21.4) [b,c,d]	411 (19.6) [b,c,d]	243 (10.7) [c,d]	84 (14.4) [d]
Depressive Symptoms	184 (11.6)	273 (26.3) [a,b,c,d]	423 (20.2) [b,c,d]	268 (11.8) [c]	88 (15.1) [d]
Depressive Ideas	148 (9.3)	246 (23.7) [b,c,d]	420 (20.1) [b,c,d]	231 (10.2) [c,d]	80 (13.7) [d]
Worry	572 (36.1)	613 (59.2) [a,b,c,d]	1064 (50.9) [b,c,d]	941 (41.5) [c,d]	260 (44.8) [d]
Anxiety Symptoms	327 (20.6)	467 (45.0) [a,b,c,d]	809 (38.7) [b,c,d]	550 (24.3) [c,d]	187 (32.2) [d]
Phobias	93 (5.9)	166 (16.0) [a,b,c,d]	250 (11.9) [b,c,d]	151 (6.7)	45 (7.7) [d]
Panic	38 (2.4)	80 (7.7) [b,d]	118 (5.6) [b,d]	60 (2.6)	32 (5.5) [d]
Compulsions	112 (7.1)	170 (16.4) [b,c,d]	276 (13.2) [b,d]	158 (7.0) [c]	70 (12.0) [d]
Obsessions	215 (13.5)	232 (22.4) [a,b,c,d]	370 (17.7) [b,c,d]	282 (12.4)	82 (14.1)
Male (n = 6355)	No headaches (n = 2573)	Definite migraine (n = 145)	Probable migraine (n = 829)	Definite TTH (n = 2385)	Probable TTH (n = 423)
Somatic Symptoms	78 (3.0)	31 (21.4) [a,b,c,d]	105 (12.6) [b,c,d]	108 (4.5) [c,d]	43 (10.1) [d]
Fatigue	351 (13.6)	54 (37.2) [a,b,c,d]	294 (35.4) [b,c,d]	490 (20.5) [c,d]	114 (26.8) [d]
Concentration and Forgetfulness	180 (7.0)	34 (23.4) [a,b,c,d]	154 (18.5) [b,c,d]	188 (7.9) [c]	66 (15.5) [d]
Sleep Problems	594 (23.1)	55 (37.9) [a,b,c,d]	343 (41.3) [b,c,d]	682 (28.6) [c,d]	159 (37.3) [d]
Irritability	376 (14.6)	62 (42.8) [a,b,c,d]	252 (30.3) [b,c,d]	424 (17.8) [c,d]	104 (24.4) [d]
Worry About Physical Health	252 (9.8)	25 (17.2) [b,c,d]	153 (18.4) [b,c,d]	263 (11.0) [c]	64 (15.0) [d]
Depressive Symptoms	210 (8.2)	33 (22.8) [a,b,c,d]	132 (15.9) [b,c,d]	187 (7.8) [c]	47 (11.0) [d]
Depressive Ideas	165 (6.4)	22 (15.2) [b,c,d]	148 (17.8) [b,c,d]	164 (6.9) [c]	50 (11.7) [d]
Worry	697 (27.1)	80 (55.2) [a,b,c,d]	406 (48.9) [b,c,d]	893 (37.4) [c,d]	189 (44.7) [d]
Anxiety Symptoms	335 (13.0)	48 (33.1) [a,b,c,d]	267 (32.1) [b,c,d]	407 (17.1) [c,d]	107 (25.1) [d]
Phobias	108 (4.2)	21 (14.5) [a,b,c,d]	103 (12.4) [b,c,d]	116 (4.9)	30 (7.0) [d]
Panic	40 (1.6)	10 (6.9) [b,d]	53 (6.4) [b,d]	41 (1.7)	18 (4.2) [d]
Compulsions	182 (7.1)	32 (22.1) [a,b,c,d]	127 (15.3) [b,d]	167 (7.0)	56 (13.1) [d]
Obsessions	214 (8.3)	21 (14.5) [a,b,c,d]	137 (16.5) [b,c,d]	247 (10.3)	47 (11.0)

[a] p-value <0.05 *vs* Probable Migraine,
[b] p-value <0.05 *vs* Definite TTH;
[c] p-value <0.05 *vs* Probable TTH;
[d] p-value <0.05 *vs* No Headache, Bonferroni-corrected Chi-Square tests.

with the highest OR being observed among females with definite migraine (OR: 3.8; 95%CI: 3.1–4.55). (Supplemental Table 2).

The main findings of our adjusted models including the two-way interaction term between each headache diagnosis * sex supported the hypothesis that there is a distinct relationship between mental health symptoms and headaches (migraine and tension-type) by sex. In the Fig. 1, it was observed sex was a modifier for many associations between headache diagnoses (definite and probable migraine and TTH) and mental health symptoms such as somatic symptoms, fatigue, concentration/forgetfulness, sleep symptoms, irritability, worry, depressive ideas, depressive symptoms, anxiety symptoms, phobias, panic, and compulsions. The highest odds for the relationship between fatigue symptoms were observed in female participants with any type of headache disorder. Corroborating the main analyses, the interaction between female sex and definite migraine was associated with the following mental health symptoms: fatigue [OR: 2.97, 95% CI: (2.03, 4.34), $p < 0.001$], concentration/forgetfulness [OR: 1.62, 95% CI: (1.06, 2.48), $p = 0.025$], sleep problems [OR: 1.69, 95% CI: (1.15, 2.46), $p < 0.001$], depressive ideas [OR: 1.66, 95% CI: (1.01, 2.73), $p = 0.044$], and anxiety symptoms [OR: 1.62, 95% CI: (1.10, 2.38), $p = 0.014$]. Conversely, there were lower odds for the relationships between compulsions and definite migraine [OR: 0.64, 95% CI: (0.40, 0.99), $p = 0.047$] and probable migraine [OR: 0.76, 95% CI: (0.59, 0.98), $p = 0.037$], suggesting that this symptom is more associated with male sex in this headache subtype.

In the sensitivity analysis, we investigated the relationship between mental symptoms and main primary headaches (definite and probable migraine and TTH) considering the frequency of headache attack in the models. We found the same pattern of higher ORs for migraine than TTH, as previously reported in the main analysis for all mental symptoms, except for the relationship between obsessions and probable TTH. Fig. 2 summarizes the ORs (95% CI) controlled by the frequency of headache attacks along with other confounders (sociodemographic data, cardiometabolic comorbidities, and prophylactic medication for migraine).

In respect to the associations between headache attack frequency and somatic symptoms, there was a progressive increase in the odds of having somatic symptoms as headache attack frequency increased, regardless of headache type (Table 3).

4. Discussion

Overall mental health symptoms reported by individuals with primary headaches were fatigue, worry, and sleep problems. After adjusting for confounders, somatic symptoms, fatigue, panic, irritability, and anxiety symptoms emerged as the most relevant symptoms associated with definite migraine (highest ORs about three or higher). All associations with migraine remained unchanged after additional adjustment for the frequency of headache attacks. Among those with TTH, although in lower magnitudes, the most significant ORs above two-fold were for

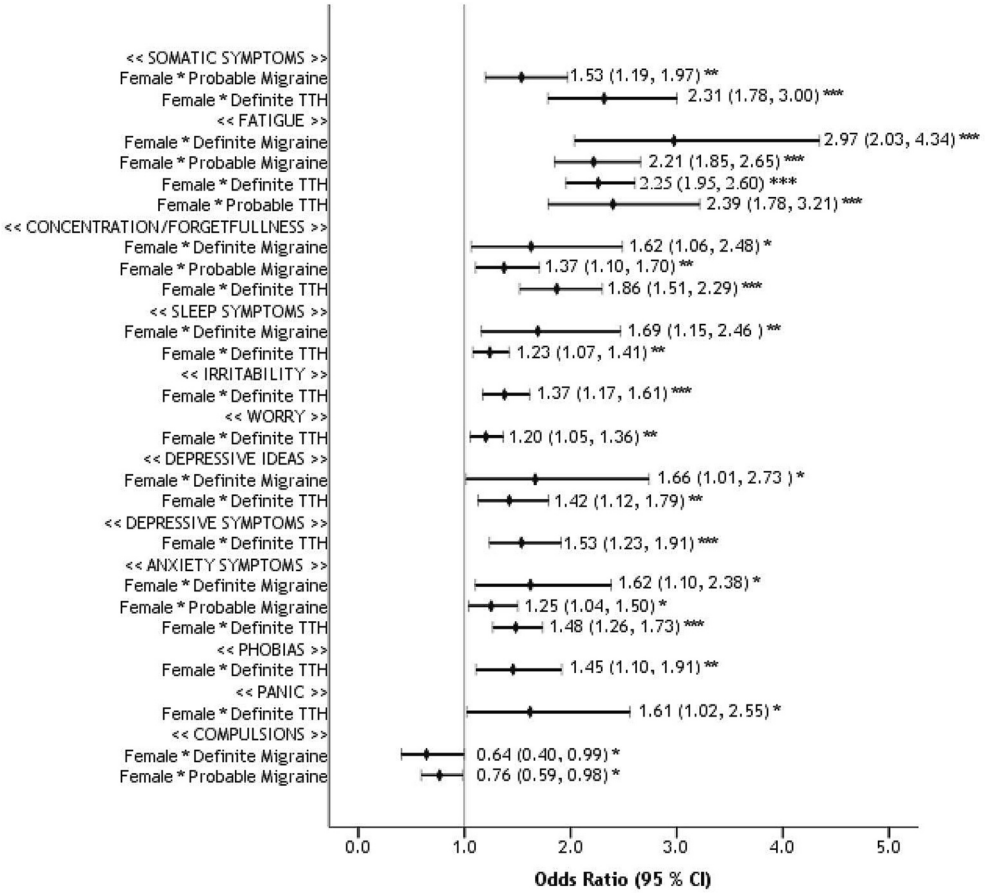

Fig. 1. Sex interactions for mental health symptoms according to headache disorders in the ELSA-Brasil study ($n = 13{,}916$).
Reference sex category: Male; *: $p < 0.05$; **: $p < 0.01$; ***: $p < 0.001$; TTH: Tension-type headache The full model included the following variables, age (continuous values), body mass index (BMI, continuous values), leisure-time and commuting physical activity levels (continuous values), smoking status (never, former, current), monthly household income (< US$1245, US$1245-3319, and > US$3319), educational level (elementary, high school, or college), self-identified skin colour (White, Black, Brown (Pardo), Other – Indigenous, Asian), and marital status (married, separated, single, widow/widower, or other), prophylactic medication (yes/no), hypertension (yes/no), diabetes (yes/no), metabolic syndrome (yes/no), and dyslipidemia (yes/no). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

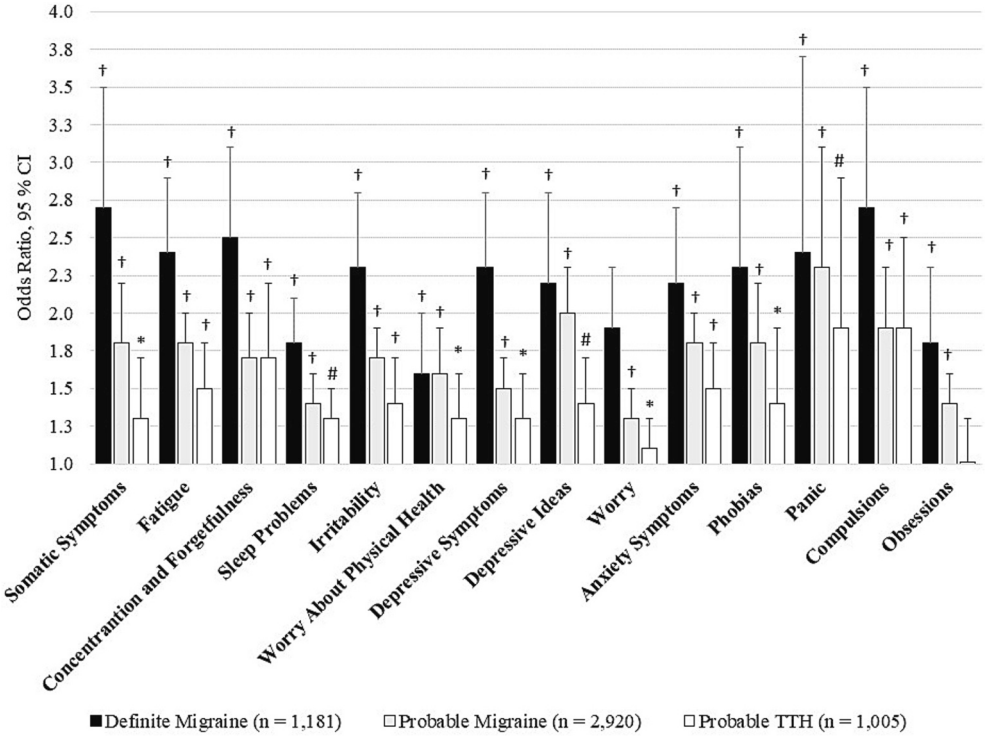

Fig. 2. ORs the associations between mental health symptoms and headache disorders after additional adjustment for headache attack frequency ($n = 9757$). *: $p < 0.05$; #: $p < 0.01$; †: $0 < 0.001$; Reference group: definite TTH ($n = 4651$). Fully adjusted model included the following variables: headache attack frequency; sex (male or female), age (continuous values), body mass index (BMI, continuous values), leisure-time and commuting physical activity levels (continuous values), smoking status (never, former, current), monthly household income (< US$1245, US$1245-3319, and > US$3319), educational level (elementary, high school, or college), self-identified skin colour (White, Black, Brown (Pardo), Other – Indigenous, Asian), and marital status (married, separated, single, widow/widower, or other), prophylactic medication (yes/no), hypertension (yes/no), diabetes (yes/no), metabolic syndrome (yes/no), and dyslipidemia (yes/no). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Table 3
Odds ratio (OR) with 95% confidence interval (CI) for the association between somatic symptoms and headache attack frequency in 9757 participants in the ELSA-Brasil study.

		1–2 times/month ($n = 2206$)	Once a week ($n = 826$)	More than once a week ($n = 1126$)	Daily ($n = 317$)
		OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Somatic Symptoms	Model 1	1.4 (1.1–1.9) [#]	2.5 (1.8–3.3) [†]	3.6 (2.7–4.7) [†]	4.9 (3.8–6.4) [†]
	Model 2	1.2 (0.9–1.6)	1.8 (1.3–2.5) [†]	2.7 (2.0–3.6) [†]	3.3 (2.5–4.3) [†]

Reference group: Once in a While ($n = 5282$). Model 1: Age- and sex-adjusted model; Model 2: Fully adjusted model, including the following variables: sex (male or female), age (continuous values), body mass index (BMI, continuous values), leisure-time and commuting physical activity levels (continuous values), smoking status (never, former, current), monthly household income (< US$1245, US$1245-3319, and > US$3319), educational level (elementary, high school, or college), self-identified skin colour (White, Black, Brown (Pardo), Other – Indigenous, Asian), and marital status (married, separated, single, widow/widower, or other), prophylactic medication (yes/no), hypertension (yes/no), diabetes (yes/no), metabolic syndrome (yes/no), dyslipidemia (yes/no), and headache types.

[#] p-value <0.01.

[†] p-value <0.001.

the associations between definite TTH and fatigue, and between probable TTH and somatic symptoms. According to the sex interaction analyses, the associations between headache disorders and mental health symptoms were stronger in females, with fatigue consistently emerging as the predominant symptom. These data may have clinical implications in terms of sex-specific headache management and care in general, and more particularly for psychotherapy. However, these findings should be confirmed in prospective studies to confirm possible sex- and headache subtype-specific mental health profile.

Few observational studies have explored a mental symptom-based approach for primary headaches, mostly involving anxiety and depressive symptoms [10–12]. Data from a populational-based study with >2.500 adults (19–69 years) showed anxiety and depression associated with TTH compared to those without headaches. Also, it was observed a stronger relationship between high frequency of headache attacks and anxiety, but not depression [10]. A cross-sectional online survey including 782 adults aged ≥18 years adopted a similar symptom-based approach using screening scales for anxiety and depressive symptoms to report the relationship between mental health symptoms and headache disorders [11]. The authors observed worry and irritability as the main symptoms associated with migraine [11]. In the cross-sectional study by Lucchetti et al. [12], 383 individuals (≥ 18 years) were investigated regarding their anxiety and headache symptoms. As main findings, it was reported that anxiety-related symptoms, such as irritability, difficulty with sleep, concentration problems, muscle tension, and fatigue had similar prevalence to ICHD-2 headache criteria, unilateral pain, and nausea for migraine and chronic migraine, regardless of a full diagnosis of anxiety [12].

It is worth mentioning biopsychosocial complexity of primary headaches, particularly migraine, is involved with feelings such as

worry, fear, anger, and frustration [13,36]. A cross-sectional study, which compared patients without psychiatric disorders and healthy controls regarding episodic and chronic migraine, identified specific psychological symptoms associated with migraine, especially anxiety, sleeping problems, and pain catastrophizing [37]. In our study, the relationship between sleep problems and headaches was still significant after the full adjustment, mainly among females with definite migraine. Although sleep complaints in migraine comorbidity are more difficult to appreciate in cross-sectional studies such as ours, a previous study has reported sleep problems (lifetime sleep problems, inadequate sleep, and difficulty falling asleep) about two to three-fold times higher in adults with migraine compared to those without migraine [38]. Possible causal mechanisms associated with sleep complaints can be justified by the night or early morning time of migraine attacks or even the lack of sleep provoked by the migraine attack [39,40].

From the clinical practice's perspective, our findings support the addition of psychological management as a non-pharmacological treatment of major headache disorders and expand the concept of psychiatric and headache disorders as comorbidities to a more granular view of mental health symptoms instead of a formal psychiatric diagnosis according to ICD-10 (International Classification of Diseases) [41] based on the CIS-R [22].

We provide evidence for a similar pattern of stronger associations with anxiety-related symptoms than depression-related symptoms as observed in migraine and TTH. However, by exploring the spectrum from TTH to migraine, we found a gradual increase in the magnitude of associations for all mental health symptoms. Likewise, anxiety-related symptoms were more associated with migraine than "tension"-type headache. These findings might have diagnostic and therapeutic implications in clinical settings. For example, the intuitive link between "tension" symptoms and "tension"-type headache may lead to migraine underdiagnoses. It is worth noting that our data, showing the spectrum from TTH to migraine and the increasing magnitude of associations for mental health symptoms, highlights the nuanced differences in the mental health impacts of various headache types. These findings may translate into different approaches to patient management with headache disorders and mental health symptoms. This broader approach involving mental health symptoms as part of headache comorbidity should be emphasized in continuing educational programs to minimize this knowledge gap [42,43].

Previous literature, including data from systematic reviews, has found more psychiatric conditions in chronic migraine than episodic migraine [44–48]. Although we did not assess chronic migraine, our findings give further insights into the relation of mental health symptoms by the stronger associations of most mental health symptoms with migraine even considering the headache frequency in our multivariate models.

Present findings point out the need for future studies employing a symptom-based approach to better elucidate three possibilities as the underlying mechanisms in this intricate relationship between mental health symptoms and headache disorders may be multifactorial. For example, the exacerbation of mental health issues due to headaches might be a direct result of neurochemical imbalances caused by migraine attacks. On the other hand, mental health conditions triggering migraines might be explained by stress-induced activations in migraine pathways. Lastly, shared genetic or environmental predispositions might provide insights into why both headache and mental health comorbidities manifest simultaneously.

4.1. Strengths and limitations

Our results corroborated previous studies that used similar symptom-based strategies [10,11], while presenting unique data from a larger admixture sample derived from a multicenter cohort study performed in Latin America [17]. The ELSA-Brasil study is a large ongoing cohort with robust data collected using standardized protocols, performed under strict quality control, including those regarding mental health and headaches in both sexes [19]. The diagnosis of headaches was based on the International Classification of Headache Disorders [1,30]. Also, mental health symptoms were extracted from a validated tool for mental health diagnoses, the CIS-R [23,28]. Our study provides evidence for a strong relationship between all mental health symptoms and migraine and TTH. Moreover, including probable TTH (a TTH with few migrainous features) in the major primary headache diagnoses makes the range of the migraine-TTH spectrum more evident and provides a clear and consistent decrease in the odds ratio of all mental health symptoms as migraine moved to TTH in the spectrum [4,5,49]. Our findings suggest a possible link between migraine diagnosis, mental health, and headache disorder comorbidity, but further research is needed to fully understand the underlying biologies involved in this comorbidity.

This study has some limitations that should be stated. The lack of evaluation of specific diagnostic criteria for the chronic forms of these headache types is due to respondents' use of categorical response options instead of specifying the number of days. Furthermore, focusing on individual symptoms may overlook the complex interactions and contextual factors influencing mental health. The measurement of mental health symptoms may not be perfect. Different symptoms might be measured with varying degrees of reliability and validity, introducing measurement error into the analysis. Mental health is often a complex construct, and a symptom-by-symptom approach may oversimplify the analysis. Some symptoms may be more meaningful when considered in conjunction with others, and a symptom-by-symptom approach may not capture the clinical relevance of certain symptom clusters or patterns. Clinically meaningful groupings may be overlooked. However, this research group is currently working on these data applying a more adequate approach to determine cluster symptoms related to headache disorders.

Although the cross-sectional design of the present study does not allow us to establish a causal link between each mental health symptom and the main primary headaches, we hypothesize that mental health symptoms can potentially correspond to real comorbidity, which can impact the headache disorder. Our findings corroborate this hypothesis since most associations remained consistent after controlling for the effects of cardiometabolic comorbidities and medication with prophylactic actions on cardiovascular diseases, mental health problems, and migraine. The ELSA-Brasil study comprises a sample with higher educational attainment and monthly income compared to the same sociodemographic indicators from the Brazilian population. This fact could compromise the external validity of our findings. However, some associations between headaches and mental health symptoms, particularly migraine-anxiety comorbidity, were also reported by other studies as we did here [50,51].

Since ELSA-Brasil enrolment included participants within the aging range from 35 to 74 years at baseline, associations between primary headaches and mental health symptoms cannot be extrapolated to individuals under 35 years of age who frequently report primary headaches and anxiety [51].

Moreover, some cautions should be taken regarding the interpretation of the high frequencies of many mental health symptoms among primary headaches, due to differences in age and sex across the headache groups.

In light of our findings, we can raise the hypothesis that the connection between migraine and mental health symptoms might not merely be correlational but might have underlying shared pathways. The stronger associations we found with anxiety-related symptoms, as opposed to depressive symptoms can suggest that stress-reactivity mechanisms may be especially pertinent in migraine sufferers. Thus, future prospective studies are required to explore this intricate relationship between headaches and mental health symptoms from a broader perspective.

Even though the analyzed data was collected before COVID-19, it is

worth mentioning that in the ELSA-Brasil study, CIS-R measurements of total psychiatric symptoms scores did not significantly change over comparing pre-pandemic ELSA-Brasil assessments in 2008–2010 (wave-1), 2012–2014 (wave-2), 2016–2018 (wave-3) and three pandemic assessments performed in 2020 in São Paulo Research Center (COVID-19 waves in May–July, July–September, and October–December) [52]. In fact, it was observed a decrease in depressive symptoms and anxiety symptoms along the three waves of COVID (all p-values <0.001). Maybe these findings reflect the higher socioeconomic by the maintenance during the pandemic of the salary guarantee of the university's participants, who are employees or retired from the university. [52].

Lastly, it has been described the effect of SARS-Cov-2 acute infection more frequently triggering or worsening primary headache disorders compared to the general population. [53]. Of note, data about COVID-19 and headaches are being collected in the ELSA-Brasil.

4.2. Conclusions

All mental health symptoms were positively associated with headache disorders in the Migraine-TTH spectrum with a clear trend toward definite migraine. Anxiety-related symptoms were more strongly associated with all headache subtypes than complaints of depressive symptoms. Particularly, tension-related symptoms such as worry and irritability were more associated with migraine than TTH. Taken together, these findings suggest that an early diagnosis and better management considering anxiety-related symptoms may have implications for the migraine-TTH spectrum. Future prospective investigations might clarify the predominant direction and the role of each mental health symptom, psychiatric diagnosis, headache diagnosis, and headache features in this context.

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CRediT authorship contribution statement

Juliane Prieto Peres Mercante: Writing – review & editing, Writing – original draft, Methodology, Investigation, Formal analysis, Conceptualization. **Arão Belitardo de Oliveira:** Writing – review & editing, Software, Methodology, Formal analysis, Data curation. **Mario Fernando Prieto Peres:** Writing – review & editing, Supervision, Formal analysis, Conceptualization. **Yuan-Pang Wang:** Writing – review & editing, Supervision. **Andre Russowsky Brunoni:** Writing – review & editing. **Paulo Andrade Lotufo:** Writing – review & editing, Conceptualization. **Isabela Martins Benseñor:** Supervision, Investigation, Conceptualization. **Alessandra Carvalho Goulart:** Writing – review & editing, Supervision, Project administration, Methodology, Conceptualization.

Declaration of competing interest

None.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jpsychores.2024.111624.

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