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RESEARCH SUBMISSION

Associations of comorbid headache disorders and depression with leisure-time physical activity among 14,088 adults in The Brazilian Longitudinal Study of Adult Health

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Abstract

Background: While headache disorders are linked to low physical activity levels, the impact of depression on this relationship is unclear.

Objective: To assess how single and comorbid diagnoses of migraine and tension-type headache (TTH) interact with depression and leisure-time physical activity (LTPA) levels in The Brazilian Longitudinal Study of Adult Health (ELSA-Brasil).

Methods: In this cross-sectional analysis based on the ELSA-Brasil baseline data, the relationship of migraine, TTH (both assessed with the International Classification of Headache Disorders, Second Edition), and depression (assessed with the Clinical Interview Schedule–Revised) with LTPA levels (International Physical Activity Questionnaire) was investigated by employing linear regression models. Models were adjusted for sociodemographic, lifestyle, and clinical covariates, and interaction terms were created to examine additive effects of comorbid conditions.

Results: Among 14,088 participants, 54.4% (7668/14,088) were female, prevalence rates were: TTH = 39.6% (5573/14,088), migraine = 27.0% (3806/14,088), depression = 0.7% (94/14,088), depression + TTH = 1.1% (148/14,088), and depression + migraine = 2.5% (356/14,088). The mean (standard deviation) LTPA levels across the groups were: no headache + no depression = 148.7 (183.0) min/week, TTH = 133.5 (170.1) min/week, migraine = 110.3 (154.8) min/week, depression = 76.5 (146.3) min/week, depression + TTH = 84.5 (127.7) min/week, and depression + migraine = 64.3 (123.2) min/week. Negative associations were found for depression ($\beta = -55.1$, 95% confidence interval [CI] −93.6 to −17.0; $p = 0.005$), migraine ($\beta = -24.7$, 95% CI −33.2 to −15.4; $p < 0.001$), and TTH ($\beta = -15.5$, 95% CI −23.1 to −7.6; $p < 0.001$) with LTPA. No interaction effect was observed for depression + TTH ($\beta = 36.0$, 95% CI −12.6 to 84.6; $p = 0.147$) and depression + migraine

Abbreviations: BMI, body mass index; CI, confidence interval; CIS-R, Clinical Interview Schedule–Revised; CPA, commuting physical activity; ELSA-Brasil, The Brazilian Longitudinal Study of Adult Health; GAD, Generalized Anxiety Disorder; ICD-10, International Statistical Classification of Diseases and Related Health Problems, 10th edition; ICHD-2, International Classification of Headache Disorders, Second Edition; IPAQ, International Physical Activity Questionnaire; LTPA, leisure-time physical activity; SD, standard deviation; TTH, tension-type headache; VIF, variance inflation factor.

($\beta = 31.7$, 95% CI −11.3 to 74.7; $p = 0.149$), indicating no additive effect of comorbid conditions on LTPA levels. After adjusting for headache attack frequency, only depression + migraine remained negatively associated with LTPA ($\beta = -38.7$, 95% CI −71.6 to −5.8; $p = 0.021$).

Conclusions: Headache disorders and depression were independently and inversely associated with LTPA, with the strongest effects seen in depression alone or comorbid with migraine.

Plain Language Summary

In this study with >14,000 people, we found that headache disorders and depression were independently associated with lower self-reported levels of physical activity (PA) in patients' leisure time. Specifically, tension-type headache, migraine, and depression were related to a reduced weekly amount of PA of ~15, 25, and 55 min, respectively, compared to people without these conditions. We found that having a headache disorder and co-occurring depression did not further reduce PA levels, suggesting that depression may be the most impactful condition that affects PA; this information may be helpful to healthcare professionals who make recommendations about PA for people with headache disorders.

KEYWORDS
health risk behaviors, healthy lifestyle, migraine, physical activity, tension-type headache; depression

INTRODUCTION

The primary headache disorders, namely migraine and tension-type headache (TTH), are widely prevalent and constitute a leading cause of disability worldwide.[1] In Brazil, the prevalence of migraine and TTH has been estimated to be around 15.8% and 29.5%, respectively, with a female-to-male sex ratio of 2.2:1 for migraine and 0.6:1 for TTH.[2,3] These disorders are associated with a substantial economic burden on society, disrupting people's quality of life during their most productive years.[4–6] Furthermore, headache disorders, especially migraine subtypes, are associated with unhealthy lifestyle behaviors such as physical inactivity.[7–9]

Headache disorders have a controversial relationship with leisure-time physical activity (LTPA). Cross-sectional studies from both population-based and large cohort surveys have reported an inverse association between self-reported LTPA levels and the prevalence of migraine[10–12] and TTH.[9] Additionally, population-based studies with data from self-reported LTPA levels[13] and daily step counts measured by wearable devices,[14] indicated a lower risk and lower incidence of migraine associated with higher LTPA levels or daily step counts. While being physically active may prevent headache disorders, the prevailing interpretations of these studies do not rule out reverse causality and assume a bidirectional relationship, wherein headache disorders may preclude LTPA participation.[8,10,13,14]

Moreover, prevalent comorbidities such as headaches and depression can have more interference with the levels of physical activity. Cross-sectional studies have shown that primary headache disorders are often comorbid with a diagnosis of depression, and depressive symptoms are more frequent in people with headache disorders.[15–20]

In a recent analysis of the National Health Survey (2013)[7] including Brazilian adults with headache-related disabilities, a poor lifestyle and mental health profile was observed, primarily characterized by depressive symptoms and low LTPA levels. Moreover, depression can represent a risk factor for chronic migraine.[21] Taken together, previous evidence suggests an additional impact of comorbid conditions associated with low LTPA levels.

While it is well-documented that depression or depressive symptoms have also been inversely associated with LTPA levels,[22,23] to date, the influence of the coexisting diagnoses such as headache disorders and depression on LTPA levels has not been assessed. The intertwined relationship of these conditions, especially depression, with physical activity behavior has been appraised by several neurobiological, psychosocial, and cognitive theories.[24–31] Depression can disrupt hedonic, mental, and motivational aspects of physical activity behavior.[26,27,32] Migraine is canonically linked to exercise avoidance as a criterion for migraine diagnosis is the worsening of head pain by routine physical effort,[33] and some patients believe exercise can precipitate migraine attacks.[30,31,34]

Therefore, we aimed to examine the association of headache disorders alone and comorbid with depression with LTPA levels in a large cohort of middle-aged individuals, The Brazilian Longitudinal

Study of Adult Health (ELSA-Brasil). We wondered whether there could be a different magnitude of association of headache disorders alone and combined with depression, with LTPA levels.

Given the respective perennial versus recurrent characteristics of depression and headache disorders, our hypotheses were that headache disorders and depression would be independently and inversely associated with LTPA levels and a depression diagnosis would imprint a stronger negative association increasing the strength of negative association with LTPA levels when comorbid with headaches. Furthermore, based on the avoidance behavior and the disability imposed by higher headache attack frequency on LTPA participation, we expected that headache attack frequency would influence the additive effect of comorbid conditions in reducing LTPA levels.

METHODS

Study design and population

This study is a secondary, post hoc analysis of baseline data collected from the ELSA-Brasil study (2008–2010), where we cross-sectionally evaluated Wave 1 (2008–2010).[35] No statistical power calculation was conducted for this analysis, and the sample size was based on the available data. In brief, ELSA-Brasil is a large ongoing multicenter cohort, designated to investigate several lifestyle and risk factors associated with cardiovascular disorders and diabetes in a sample of 15,105 civil servants (aged 35–74 years) from six metropolitan areas of Brazil: São Paulo, Rio de Janeiro, Belo Horizonte, Salvador, Porto Alegre, and Vitória.[35] Although the primary aim of ELSA-Brasil is to investigate cardiometabolic diseases, the study has also assessed other comorbidities, including headache disorders. A previous report on other aspects of the relationship between LTPA and headache disorders in the ELSA-Brasil study can be found elsewhere.[8]

Baseline data for biochemical sampling and assessments were performed in workplace-based interviews, and clinic visits were all conducted between August 2008 and December 2010.[35] The inclusion criteria were participants of both sexes (male or female, assigned at birth), active or retired employees aged 35–74 years.

Exclusion criteria were current or recent pregnancy (<4 months before the interview), intention to quit a job soon, severe cognitive or communication impairment, and retired participants living outside the study center's corresponding metropolitan area. Exclusion criteria also included participants with secondary headaches or unclassified primary headaches, meaning headache disorders that did not meet criteria for any disorder entity, and excluding secondary causes.[36]

Approvals from all institutional review boards (CEP-HU/USP: #659/06) and National Research Ethics Committee (CAAE: #08109612.7.1001.0076), as well as signed informed consent forms were provided. This study complies with the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) guidelines for reporting data from observational research.

Outcome variable

Physical activity levels

The long-form of the International Physical Activity Questionnaire (IPAQ) was adopted to collect data on LTPA and commuting physical activity (CPA) levels in the ELSA-Brasil study. The IPAQ was previously translated and validated in Brazil.[37] Acceptable criterion validity (pooled $\rho_{Spearman}=0.30$) against an accelerometer (CSA model 7164) across 12 countries (including Brazil) has been shown for the form used here.[37] When compared to physical activity measured by an accelerometer, the IPAQ presented good convergent validity for overall physical activity ($r_{Spearman}=0.55$) and vigorous physical activity ($r_{Spearman}=0.71$), and a smaller yet significant relationship for moderate physical activity ($r_{Spearman}=0.21$).[38]

The IPAQ assesses the physical activity levels in the past 7 days. Within the LTPA domain, the IPAQ enquires about physical activity levels of moderate and vigorous intensity related to recreation, sport, exercise, or leisure (e.g., *during the last 7 days, how many days did you do moderate physical activities in your leisure time?*). In the CPA domain, the IPAQ assesses moderate-intensity bicycling and walking related to travel to and from work, doing errands, or going from place to place (e.g., *during the last 7 days, how many days did you walk from place to place?*). Physical activity levels were computed by multiplying the weekly frequency (number of days) by the duration (min/day) of the physical activity performed and expressed as min/week. In the present analyses, we evaluated LTPA as an outcome variable. As CPA may affect the main comorbidities differently, models were adjusted by this domain..[8,12,39]

Exposure variables

Depression

Depression diagnosis was determined through the Clinical Interview Schedule–Revised (CIS-R). We used the version adapted to Brazilian Portuguese,[40] which was applied by trained interviewers from the ELSA-Brasil study. In brief, the CIS-R assesses 14 symptomatic clusters of depression and anxiety in the previous 7 days, namely somatic complaints, fatigue, concentration and forgetfulness, sleep disturbance, irritability, worry about physical health, depression, depression ideas, worry, anxiety, phobias, panic attacks, compulsions, and obsessions. Scores range from 0 to 4 for each subscale, except for depression ideas which range from 0 to 5. The relevant symptoms, defined as participants who scored ≥2 on the corresponding subscales, are grouped to form diagnoses based on the International Statistical Classification of Diseases and Related Health Problems, 10th edition (ICD-10). Participants with depression were all those coded with F32.[40]

Headache disorders

All participants in the ELSA-Brasil baseline evaluation ($N = 15,105$) who answered "yes" to the probe question, "In the last 12 months, did you have a headache?" were invited to respond to a detailed headache questionnaire based on the International Classification of Headache Disorders, Second Edition (ICHD-2) (Headache Classification Subcommittee of the International Headache Society, 2004). We used a version of ICHD previously validated in Brazil.[41] Briefly, the questionnaire investigates pain frequency, duration, quality, location, intensity, triggering factors, and accompanying symptoms such as nausea or vomiting. The reported headache characteristics were based on the participants' main headache type according to the methodology employed by epidemiological studies on headache disorders.[42–45] Participants fulfilling all criteria for migraine and TTH were classified according to the ICHD-2. If participants fulfilled all but one criterion for migraine or TTH, they were classified as probable migraine or probable TTH, respectively.[36] Data on headache attack frequency were collected through closed-ended questions with the following response options: "once in a while," "one to two per month," "once a week," "more than once a week," and "daily."

Covariates

Demographic and clinical variables

To control for the effects of variables that recognizably affect LTPA participation, such as socioeconomic profile, sex, age, body mass index (BMI), other physical and mental health comorbidities,[46,47] as well as prescribed medication with dual effects on migraine and other clinical conditions (e.g., hypertension, anxiety, etc.) that could affect the predisposition and ability to engage in LTPA, such as antidepressants, anxiolytic drugs, we included in the adjusted models sociodemographic, clinical, and pharmacological treatment as covariate variables. Sociodemographic variables were sex assigned at birth; age (continuous); BMI (continuous); monthly household income (<US$1245, US$1245–3319, and >US$3319); educational level (Elementary, High School or College); self-reported race: White, Brown, Black, and Others (Asian, Indigenous, or Native); marital status (Married, Separated, Single, Widow/Widower, or Other); and smoking status (Never, Former, Current).

Based on standardized anthropometric and laboratory procedures,[48] we collected data on cardiometabolic comorbidities, including blood pressure, fasting glycemia, total cholesterol and its components, triglycerides, glycosylated hemoglobin, insulin, and Homeostasis Model Assessment of Insulin Resistance (HOMA-IR) index. The diagnosis of hypertension was considered among participants with a previous medical history of high blood pressure who met the criteria of systolic blood pressure ≥140 mmHg, and/or diastolic blood pressure ≥90 mmHg, or who were under medication for hypertension. Similarly, diabetes diagnosis was based on a combination of medical history, medication use, and specific thresholds for fasting plasma glucose (≥126 mg/dL), 2-h plasma glucose (≥200 mg/dL), or hemoglobin A1C levels (≥6.5%). Dyslipidemia, metabolic syndrome, and obesity were defined according to established criteria of the National Cholesterol Program-Adult Treatment Panel III guidelines for dyslipidemia and metabolic syndrome.[49]

The migraine prophylactic medication classes considered in this study were selected according to the American Academy of Neurology guidelines as follows: Level A antiseizure drugs (divalproex sodium, sodium valproate, topiramate), and beta-blockers (propranolol, metoprolol, timolol); Level B antidepressants (amitriptyline, venlafaxine) and beta-blockers (atenolol, nadolol).[50]

Generalized Anxiety Disorder (GAD), diagnosis was determined by the CIS-R and ICD-10 criteria. Diagnosis of depression as described above and anxiety disorders were labeled with ICD-10 codes F41.1, F41.0, F40.1, or F42.

Statistical analysis

Baseline characteristics related to socioeconomic, clinical, and LTPA data were reported as a percentage (%) for categorical and mean (standard deviation [SD]) for continuous variables. Between-groups comparisons were performed by chi-squared test (categorical variables) or one-way analysis of variance with Bonferroni corrections.

In this study, we used general linear models to examine the relationship between the headache disorders and depression and LTPA. To test the individual and additive effects of the exposure variables, headache diagnosis (none, TTH, migraine) and depression diagnosis (none, present) entered the models as single factors and as the product of the interaction between headache and depression (e.g., headache diagnosis, depression, and headache diagnosis × depression).

Unstandardized β coefficients and R^2 statistics were computed and considered as estimates of the associations between headache diagnosis alone and comorbid with depression and LTPA levels expressed in min/week (continuous variable).

Crude and adjusted (sex, age, BMI, household income, educational attainment, self-reported race, marital status, smoking status, CPA, use of migraine prophylactic medication, GAD, hypertension, diabetes, metabolic syndrome, and dyslipidemia) models were generated. In the main analyses, probable and definite cases were pooled together for each headache type (TTH and migraine).

To further investigate the associations of definite cases of headache disorders and depression with LTPA levels, we ran two sensitivity analyses employing the same general linear models approach. In the first, we excluded probable migraine ($n = 2850$) and probable TTH ($n = 1022$), leaving a sample size of 10,216 participants. In the second, we investigated whether adding the headache attacks frequency (categories "once in a while," "one to two per month," "once a week," "more

than once a week," and "daily") would influence the associations of headache disorders and depression on LTPA levels. A linear regression model added the headache attack frequency in the adjusted models with only participants with definite cases of headache disorders ($n = 6011$). In this analysis, the TTH group was the reference group as it was the most prevalent headache type and associated with lower levels of headache attack frequency (i.e., "once in a while").

In all the adjusted models, the previously referenced sociodemographic variables were entered into the regression equations with the following additional variables: use of prophylactic medication (yes/no), CPA levels (continuous), diagnosis of GAD (yes/no), hypertension (yes/no), diabetes (yes/no), metabolic syndrome (yes/no), and dyslipidemia (yes/no).

For the potential impact of multicollinearity on the estimate accuracy, we calculated variance inflation factor (VIF) and Pearson (r) bivariate correlations. Multicollinearity issues were assumed if variables were highly correlated (values of VIF: ≥10 and r ≥0.7). In the linear regression models, there was no evidence of multicollinearity issues as indicated by the values of VIF being <2.0 and significant r values being <0.1, both of which are considered acceptable levels. A two-tailed $p < 0.05$ was used to determine statistical significance for all tests. All statistical analyses were conducted using Stata software (version 17.0, StataCorp LLC).

RESULTS

Of 15,105 ELSA-Brasil participants at baseline, 14,088 provided complete data for the main analyses presented here. Figure 1 shows a flowchart of the sampling procedure in the study, including the core and sensitivity analyses.

The mean age (95% confidence interval [CI]) of participants was 52.1 (51.9–52.2) years, 54.4% (7668/14,088) were female, 51.9% (7311/14,088) were White, and 52.5% (7394/14,088) had a college degree. Overall, participants with headache disorders were predominantly younger females of middle-income strata who had a higher frequency of mental health disorders but a lower frequency of cardiometabolic comorbidities, as well as lower LTPA levels, and who used more migraine preventive medications than their counterparts without headache disorders (Table 1).

The frequencies of headache disorders and depression, alone or in comorbid subgroups, were: no headache + no depression = 29.2% (4111/14,088), only TTH = 39.6% (5573/14,088), only migraine = 27.0% (3806/14,088), only depression = 0.7% (94/14,088), depression + TTH = 1.1% (148/14,088), and depression + migraine = 2.5% (356/14,088). The frequency of definite cases of migraine was 9.3% (1312/14,088), and TTH was 33.3% (4699/14,088). Group differences were observed in the LTPA levels

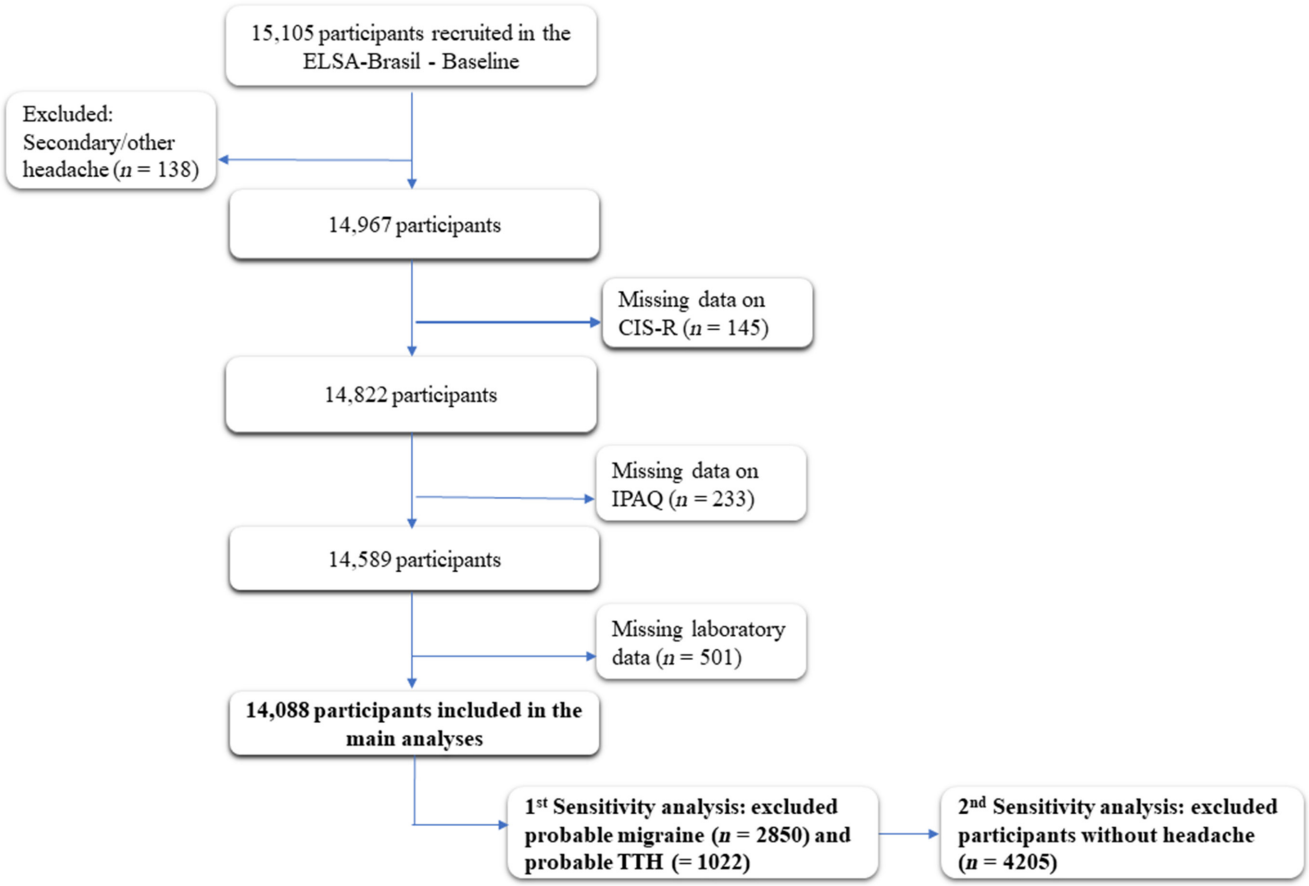

FIGURE 1 Flow chart of participants in The Brazilian Longitudinal Study of Adult Health (ELSA-Brasil) study. CIS-R, Clinical Interview Schedule – Revised; IPAQ, International Physical Activity Questionnaire; TTH, tension-type headache.

TABLE 1 Sociodemographic and clinical characteristics of 14,088 participants in the baseline from The Brazilian Longitudinal Study of Adult Health (ELSA-Brasil) study.

Characteristic	Groups			*p*
	No headache (*n* = 4205)	TTH (*n* = 5721)	Migraine (*n* = 4162)	
Age, years, mean (SD)	55.6 (9.3)	51.2 (8.8)	49.8 (8.0)	<0.001
BMI, kg/m^2, mean (SD)	27.1 (4.7)	26.9 (4.6)	27.0 (4.9)	0.027
Sex, *n* (%)				
Female	1606 (38.2)	2886 (50.4)	3176 (76.3)	<0.001
Ethnicity—self-reported, *n* (%)				
White	2095 (49.8)	3115 (54.4)	2101 (50.5)	<0.001
Brown	1202 (28.9)	1572 (27.5)	1215 (28.9)	
Black	722 (17.3)	840 (14.7)	725 (17.2)	
Other (Yellow, Indigenous, or Native)	137 (3.3)	194 (3.4)	170 (4.0)	
Education, *n* (%)				
Primary	735 (17.5)	630 (11.0)	450 (10.8)	<0.001
High school	1412 (33.6)	1825 (1.9)	1642 (39.5)	
College	2058 (48.9)	3266 (57.1)	2070 (49.7)	
Household income, *n* (%)				
<US$1245	1199 (28.5)	1339 (23.4)	1213 (29.1)	<0.001
US$1245–3319	1727 (41.1)	2505 (43.8)	1955 (47.0)	
>US$3319	1279 (30.4)	1877 (32.8)	994 (23.9)	
Marital status, *n* (%)				
Married	2841 (67.6)	3858 (67.4)	2629 (63.2)	<0.001
Separated	646 (15.4)	893 (15.6)	745 (17.9)	
Single	407 (9.7)	573 (10.0)	442 (10.6)	
Widowed	192 (4.6)	202 (3.5)	192 (4.6)	
Other	154 (3.7)	195 (3.4)	117 (2.8)	
Current smoking, *n* (%)	590 (14.0)	694 (12.1)	545 (13.1)	<0.001
Clinical comorbidities, *n* (%)				
Depression	94 (2.2)	148 (2.6)	356 (8.6)	<0.001
GAD	297 (7.1)	626 (10.9)	927 (22.3)	<0.001
Hypertension	1851 (44.0)	1943 (34.0)	1272 (30.6)	<0.001
Diabetes	1106 (26.3)	1007 (17.5)	660 (15.9)	<0.001
Dyslipidemia	2823 (67.1)	3586 (62.7)	2607 (62.6)	<0.001
Metabolic Syndrome	533 (13.2)	601 (10.5)	508 (12.2)	<0.001
Headache attack frequency, *n* (%)				
Once in a while	–	3776 (66.1)	1569 (37.8)	<0.001
1–2 times/month	–	1056 (18.5)	1178 (28.4)	
Once a week	–	389 (6.8)	446 (10.7)	
More than once a week	–	394 (6.9)	740 (17.8)	
Daily	–	100 (1.7)	222 (5.3)	
Preventive drug use, *n* (%)	207 (4.9)	352 (6.2)	409 (9.8)	<0.001
Physical activity levels				
LTPA, mean (SD) min/week	156.5 (212.3)	137.8 (189.9)	109.9 (165.9)	<0.001
CPA, mean (SD) min/week	180.9 (295.4)	154.4 (268.0)	150.8 (233.8)	<0.001

Note: Hypothesis tests for continuous and categorical variables were one-way analysis of variance and chi-square test.

Abbreviations: BMI, body mass index; CPA, commuting physical activity; Depression, major depressive disorder; GAD, Generalized Anxiety Disorder; LTPA, leisure-time physical activity; SD, standard deviation; TTH, tension-type headache; US$, United States dollar.

(F[14,082, 5] = 34,797, η^2 = 0.012, p < 0.001). Compared with the no headache + no depression group, all the remaining groups showed lower LTPA levels (Figure 2). The pairwise post hoc analysis showed that the depression + migraine group (p < 0.001), but not depression alone (p = 0.896), or depression + TTH (p > 0.999) groups presented with lower LTPA levels than the migraine group (Figure 2).

In the crude models, there were significant inverse associations between headache disorders and depression with LTPA levels, which all remained significant in the adjusted models. The adjusted model showed significant inverse associations of TTH (β = −15.58, 95% CI −23.15 to −7.68; p < 0.001), migraine (β = −24.73, 95% CI −33.29 to −15.45; p < 0.001), and depression (β = −55.16, 95% CI −93.69 to −17.05; p = 0.005), but no significant interaction effects of comorbid depression + TTH (β = 36.01, 95% CI −12.61 to 84.64; p = 0.147), or depression + migraine (β = 31.70, 95% CI −11.32 to 74.73; p = 0.149) (Table 2). Based on the unstandardized β coefficients, people with TTH, migraine, and depression engage in ~15, 25, and 60 min less weekly LTPA, respectively, compared to those in the no headache + no depression group (Table 2). In this model and based on the R^2 statistics, 5.8% of the variance in LTPA was explained by headache disorders and depression.

These results were confirmed in the sensitivity analysis, excluding probable TTH (n = 1022) and probable migraine (n = 2850) cases. There were significant inverse associations of TTH (β = −14.71, 95% CI −23.47 to −6.48; p = 0.001), migraine (β = −26.24, 95% CI −39.82 to −12.43; p < 0.001), depression (β = −56.01, 95% CI −96.20 to −15.81; p = 0.006), but no significant interaction effects of comorbid depression + TTH (β = 30.2, 95% CI −24.3 to 84.9; p = 0.278) and depression + migraine (β = 26.7, 95% CI −28.3 to 76.5; p = 0.368) with LTPA levels in the adjusted model.

Finally, regarding the influence of headache attack frequency, only comorbid depression + migraine (β = −38.7, 95% CI −71.6 to −5.8; p = 0.021) was associated with significantly lower LTPA levels compared to the TTH group after adding headache attack frequency in the adjusted models (Table 3). These findings indicate that headache frequency had an effect in reducing LTPA levels for migraine alone and when TTH is comorbid with depression, whereas it did not influence the effect of comorbid depression and migraine.

DISCUSSION

In this study, we partly confirmed our hypotheses that major headache disorders and depression were independently and negatively associated with LTPA levels, with depression exerting the strongest

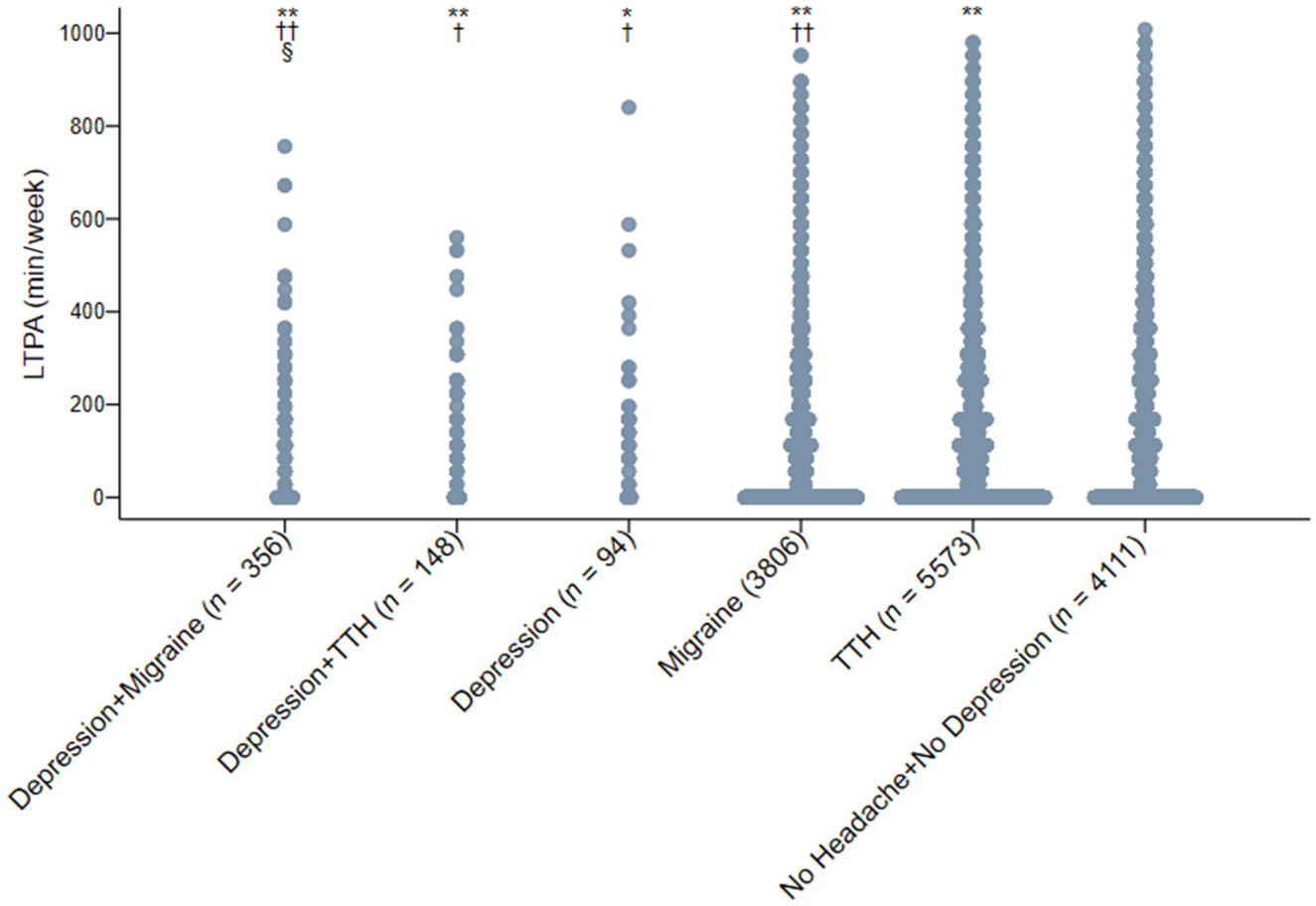

FIGURE 2 Dot plot of leisure-time physical activity levels distribution with comparisons between groups. LTPA, leisure-time physical activity; TTH, tension-type headache; *p < 0.01; **p < 0.001, versus no headache + no depression; †p < 0.05; ††p < 0.01, versus TTH; §p < 0.001, versus migraine; one-way analysis of variance pairwise comparisons adjusted by Bonferroni's post hoc tests.

TABLE 2 Unstandardized coefficients for the relationships between headache disorders (definite and probable diagnoses) and depression on leisure-time physical activity in the baseline of The Brazilian Longitudinal Study of Adult Health (ELSA-Brasil) study ($n = 14{,}088$).

	β (95% CI)	SE	p
Crude model			
Main effects			
TTH ($n = 5573$)	−19.3 (−27.0 to −11.6)	3.9	<0.001
Migraine ($n = 3806$)	−44.4 (−52.8 to −36.0)	4.2	<0.001
Depression ($n = 94$)	−81.8 (−120.7 to −42.9)	19.8	<0.001
Interaction effects of headache × depression			
Depression × TTH	−33.6 (−16.1 to 83.3)	25.3	0.185
Depression × migraine	−34.8 (−9.1 to 78.8)	22.4	0.121
Adjusted model			
Main effects			
TTH ($n = 5573$)	−15.5 (−23.1 to −7.6)	3.9	<0.001
Migraine ($n = 3806$)	−24.7 (−33.2 to −15.4)	4.5	<0.001
Depression ($n = 94$)	−55.1 (−93.6 to −17.0)	19.5	0.005
Interaction effects of headache × depression			
Depression × TTH	36.0 (−12.6 to 84.6)	24.8	0.147
Depression × migraine	31.7 (−11.3 to 74.7)	21.9	0.149

Note: Reference group: no headache + no depression ($n = 4111$); the adjusted models were controlled for the effects of sex, age, body mass index, household income, educational attainment, self-reported race, marital status, smoking status, commuting physical activity, use of medication with migraine prophylactic actions, diagnosis of generalized anxiety disorder, hypertension, diabetes, metabolic syndrome, and dyslipidemia.

Abbreviations: CI, confidence interval; SE, standard error; TTH, tension-type headache.

TABLE 3 Sensitivity analysis with unstandardized coefficients for the relationships between definite diagnoses of headaches disorders and depression on leisure-time physical activity levels adjusted for headache attack frequency in the baseline of The Brazilian Longitudinal Study of Adult Health (ELSA-Brasil) study ($n = 6011$).

	β (95% CI)	SE	p
Crude model			
Main effect			
Migraine ($n = 1173$)	−25.5 (−32.9 to −18.0)	3.7	<0.001
Interaction effects of headache × depression			
Depression × TTH ($n = 106$)	−53.2 (−89.4 to −16.9)	18.4	0.004
Depression × migraine ($n = 139$)	−70.7 (−103.2 to −38.2)	16.5	<0.001
Adjusted model			
Main effect			
Migraine ($n = 1173$)	−5.8 (−19.2 to 7.5)	6.8	0.393
Interaction effects of headache × depression			
Depression × TTH ($n = 106$)	−30.0 (−66.0 to 5.9)	18.3	0.102
Depression × migraine ($n = 139$)	−38.7 (−71.6 to −5.8)	16.7	0.021

Note: Reference group: TTH ($n = 4593$). the adjusted models were controlled for the effects of headache attack frequency, sex, age, body mass index, household income, educational attainment, self-reported race, marital status, smoking status, commuting physical activity, use of medication with migraine prophylactic actions, diagnosis of generalized anxiety disorder, hypertension, diabetes, metabolic syndrome, and dyslipidemia.

Abbreviations: CI, confidence interval; SE, standard error; TTH, tension-type headache.

association. We did not find an increase in the strength of the association of depression when comorbid with headache disorder influencing the physical activity levels. However, depression comorbid with migraine but not TTH seemed to negatively associate with LTPA levels regardless of headache attack frequency, indicating a distinct effect of headache disorders in this relationship.

The interpretation of these findings should account for the self-reported data on LTPA levels and questionnaire-based diagnosis of depression. As such, it is advisable to exercise caution when interpreting the data and drawing conclusions. Furthermore, the attenuated strength of associations (lower β coefficients) after adjustments suggests that additional, uncollected confounders may further weaken these relationships. For example, LTPA is also associated with job stress in this cohort.[51] Finally, the prevalence of migraine in the ELSA-Brasil cohort is lower compared to the general Brazilian population (9.3% vs. 15.2%, respectively). This discrepancy can be attributed to the higher mean age of the participants in this cohort relative to the general adult population.[3] The relationship between physical activity, headache disorders, and depression can be bidirectional, as already demonstrated in both cross-sectional[7,8,12,23,52] and prospective studies.[14,53,54] Population-based studies support the two opposite contentions that physical activity represents a protective factor for headache disorders and depression, whereas headache attacks and depressive symptoms could be a barrier to engaging in physical activity.[26,31,32,34]

Despite the concerns regarding causality inferences, our findings are in line with previous cross-sectional studies on the independent, inverse associations of headache disorders or depression with LTPA.[7,8,12,23,52] The strongest independent association of depression and the effect of headache attack frequency in reducing LTPA may reflect the longer-lasting characteristic of depression contrasting to the paroxysmal, cyclical feature of headache disorders and the impact of headache chronification hindering LTPA.

Beyond the interpretation of a causal link of our findings, the independent associations of depression and headache disorders have implications for clinical management and future public health policies. Owing to the high prevalence of headache disorders[2,3] and their higher association with depression,[15–20] our results underscore the need for screening headache disorders comorbid with

depression and depressive symptoms, especially migraine, while counseling healthy lifestyles and recommending exercise training or physical activity.

Abundant evidence favors the recommendation of a wide range of prescribed exercise modalities and increasing LTPA levels for optimal management of migraine[29,55–58] and mental disorders.[53,59] Data from systematic reviews and meta-analyses of randomized controlled trials suggest preventive effects of an ample array of modalities/intensities of exercise on depression and/or depressive symptoms[53,59,60] and migraine.[58,61] A prospective observational study ($n = 6042$) showed a lower incidence of migraine among participants with higher daily step counts compared to those with median values of steps during 4 years of follow-up.[14]

In line with our findings regarding the impact of headache attack frequency, in clinical practice, patients often complain of difficulties engaging in regular physical activity and usually do not adopt this lifestyle behavior as a non-pharmacological treatment option before visiting a specialized clinic.[62–64] Healthcare professionals should address these challenges by offering tailored exercise plans that account for the specific needs and limitations of individuals with comorbid headache disorders and depression.[55,65] Providing psychoeducation to patients about the therapeutic benefits of exercise, along with strategies to promote self-efficacy, self-acceptance, and to mitigate potential trigger effects, is foundational to empower them to prioritize physical activity as part of their overall pain and depression management.[31,66,67] Encouraging a feasible and personalized approach based on individual preferences and clinical characteristics can significantly improve adherence and ultimately enhance the effectiveness of exercise interventions for these populations.[55,65,67]

Importantly, we hypothesized that the associations with lower LTPA levels would be attenuated by controlling the attack frequency for both headache types when comorbid with depression. As depression was the main driver of physical inactivity in the main analyses, the lack of an influence of headache attack frequency in the migraine + depression group, as opposed to the depression + TTH group in reducing LTPA levels, may suggest a distinct effect of headache disorders when comorbid with depression. Possibly, common psychobiological mechanisms underlying depression and migraine (e.g., anhedonia, fatigue, sleep problems, avoidance, etc.) may mediate this relationship beyond the attack frequency per se. This is in line with findings of symptom-based analyses of mental health symptoms associated with migraine.[68] Conversely, as the effect of depression comorbid with TTH on LTPA levels was influenced by attack frequency, there seemed to be a paradoxical "counteracting" effect of TTH. Another explanation for these distinct effects of migraine and TTH would involve psychobiological mechanisms underlying the canonical criterion regarding the worsening or aggravation of headache by routine physical activity, a criterion and hallmark of migraine but not of TTH.[33,69] Thus, migraine but not TTH would mediate physical inactivity behavior regardless of attack frequency.[8,31,66] In fact, in clinical practice, patients with TTH often report engaging in physical activity to alleviate their headache attacks, whereas the opposite behavior is reported by patients with migraine.[70] Further studies are warranted to identify and test biopsychosocial and cognitive models of physical activity behavior in headache disorders.

Exercise-based interventions should be founded upon theoretical models that sufficiently elucidate and forecast physical activity behaviors in these populations.[55,65]

The study's strengths include its large sample size, and the comprehensive models implemented to account for potential confounding variables, which could influence the outcome variables, e.g., the migraine preventive medication, BMI, socioeconomic status, clinical diagnosis of cardiometabolic comorbidities, GAD diagnosis, and CPA levels.

The main limitation of this study is the cross-sectional data, which impedes drawing causal inferences as reverse causality cannot be ruled out. In this regard, a second wave for collecting headache data is under way and in the future the ELSA-Brasil study will provide prospective data for these associations. The ELSA-Brasil sample is not representative of the Brazilian population; it has a higher education and socioeconomic profile than the general population in this country. Thus, selection bias may be another issue for generalized assumptions of these findings. Nevertheless, this cohort has a gradient of socioeconomic status with a range of occupations classified as unskilled, technical/clerical, faculty, and professional staff, allowing us to stratify for groups across the sample. Physical activity levels and depression diagnosis were based on self-reported data, which has accepted validity but recall bias and social desirability bias cannot be ruled out. Likewise, despite being a useful tool in epidemiological research, a diagnosis of depression from the CIS-R questionnaire might not consider subtle nuances that a skilled clinician could identify. There are forms of depression in which the patient feels "slowed down" and may not even get out of bed. This effect was not controlled for, which could have led to potential inaccuracies in diagnosis. Lastly, it was not possible to evaluate the association between comorbid migraine and TTH disorders, as headache data were collected based on the characteristics of the headache type described as the main complaint by participants.

In conclusion, this study underscores the independent inverse associations of headache disorders and depression with LTPA levels, mainly of the individuals with depression who had the lowest levels of exercise in their leisure time. To better understand the intricate relationship between headache disorders, mental health conditions, and physical activity behavior, further investigations employing prospective design, the use of wearable devices that measure LTPA, and testing behavioral approaches to increase physical activity levels in this population are warranted. These studies are crucial for elucidating the effects of headache and mental health disorders on physical activity patterns and to ultimately implement strategies to reverse this negative relationship.

AUTHOR CONTRIBUTIONS

Arão Belitardo de Oliveira: Conceptualization; data curation; formal analysis; writing – original draft. **Mario Fernando Prieto Peres:**

Supervision; writing – review and editing. **Juliane Prieto Peres Mercante:** Writing – review and editing. **André R. Brunoni:** Supervision; writing – review and editing. **Yuan-Pang Wang:** Supervision; writing – review and editing. **Maria del Carmen B. Molina:** Supervision; writing – review and editing. **Lucas K. Uchiyama:** Writing – review and editing. **Paulo A. Lotufo:** Data curation; funding acquisition; project administration; supervision. **Isabela M. Benseñor:** Data curation; project administration; supervision; writing – review and editing. **Alessandra C. Goulart:** Data curation; funding acquisition; project administration; supervision; writing – review and editing.

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CONFLICT OF INTEREST STATEMENT

Arão Belitardo de Oliveira, Mario Fernando Prieto Peres, Juliane Prieto Peres Mercante, André R. Brunoni, Yuan-Pang Wang, Maria del Carmen B. Molina, Lucas K. Uchiyama, Paulo A. Lotufo, Isabela M. Benseñor, and **Alessandra C. Goulart** have no conflicts of interest to disclose.

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