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RESEARCH SUBMISSIONS

# Physical activity pattern and migraine according to aura symptoms in the Brazilian Longitudinal Study of Adult Health (ELSA-Brasil) cohort: A cross-sectional study

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## Abstract

**Objective:** To estimate the associations of physical activity (PA) levels with migraine subtypes.

**Background:** Physical activity has been associated with reduced migraine prevalence, but less is known about its relationship with migraine subtypes and PA levels as recommended by World Health Organization (WHO).

**Methods:** In this cross-sectional analysis of the Brazilian Longitudinal Study of Adult Health (ELSA-Brasil), we estimated the odds ratios (ORs) of migraine with aura (MA) and migraine without aura (MO), compared to participants without headaches, according to PA levels in the leisure time (LTPA), commuting time (CPA), and combined PA domains.

**Results:** In total, 2773 participants provided complete data, 1556/2773 (56.1%) were women, mean (SD) age of 52.3 (9.1) years. In this study's sample, 1370/2773 (49.4%) participants had overall migraine, 480/2773 (17.3%) had MA, and 890/2773 (32.0%) had MO. In the LTPA domain, there were reduced odds of MA (OR 0.72, 95% confidence interval [CI] 0.53–0.96; $p = 0.030$) and MO (OR 0.71, 95% CI 0.56–0.90; $p = 0.005$) in participants who met the WHO PA guidelines after adjustment for confounder variables. In the analyses stratified by intensity, moderate LTPA was associated with reduced odds of MA (OR 0.56, 95% CI 0.320–0.99; $p = 0.049$), while vigorous LTPA was associated with reduced odds of MO (OR 0.55, 95% CI 0.395–0.77; $p = 0.001$). There were no significant associations between migraine subtypes and CPA or combined PA domains. In the whole migraine sample, meeting the WHO PA guidelines in the LTPA (OR 0.275, 95% CI 0.083–0.90; $p = 0.034$), CPA (OR 0.194, 95% CI 0.064–0.58; $p = 0.004$), and combined domains (OR 0.115, 95% CI 0.032–0.41; $p = 0.001$) was associated with reduced odds of daily migraine attack frequency.

**Abbreviations:** CI, confidence interval; CIS-R, Clinical Interview Schedule-Revised; ELSA-Brasil, Brazilian Longitudinal Study of Adult Health; GAD, generalized anxiety disorder; ICHD-2, International Classification of Headache Disorders, 2nd edition; IPAQ, International Physical Activity Questionnaire; IQR, interquartile range; MA, migraine with aura; MO, migraine without aura; OR, odds ratio; (C)(LT)PA, (commuting) (leisure time) physical activity; SD, standard deviation; TTH, tension-type headache; WHO, World Health Organization.

  

**Conclusions:** Meeting the WHO PA guidelines for LTPA, but not CPA or combined PA domains, is associated with lower migraine occurrence. Moderate LTPA favors MA reduction, while vigorous LTPA favors MO reduction.

**KEYWORDS**
exercise therapy, migraine, migraine with aura, physical activity

## INTRODUCTION

Epidemiological studies suggest that regular physical activity (PA) is associated with lower migraine prevalence.[1–4] Nevertheless, PA and migraine do not associate in a dose–response manner, and these studies have shown heterogeneous associations regarding sex, migraine subtypes, PA domains, intensity, and modality.[1–4] Most studies have assessed PA levels only in the leisure time (LTPA) and have not considered migraine subtypes.[1–6] Less is known regarding the association of other PA domains or multidimensional PA domains (i.e., combining specific PA domains) with migraine with aura (MA) and without aura (MO). Only one study investigated the associations between PA levels and MA, also suggesting different associations regarding sex and PA intensity/domains.[3]

Besides the LTPA (e.g., recreational social and individual sports, gym group classes, weightlifting, bodyweight exercises, etc.), PA in the transportation/commuting time (CPA), such as walking and cycling for transport to/from work, or while doing errands, has also been associated with lower risk of cardiovascular diseases, cancer, and mortality.[7–9] However, there is no study investigating the relationship between CPA and MA to date.

In a previous cross-sectional analysis of the Brazilian Longitudinal Study of Adult Health (ELSA-Brasil) cohort, we found that, compared to people meeting the World Health Organization (WHO) PA guidelines for LTPA, physical inactivity in the LTPA domain was associated with higher migraine and tension-type headache (TTH) occurrence.[10] Physical inactivity related to the CPA domain is associated with higher TTH in men and lower migraine in women. Physical inactivity within vigorous LTPA intensity, but not moderate LTPA, is associated with higher migraine, mostly in women. Finally, physical inactivity was associated with higher headache attack frequency.[10]

The current World Health Organization (WHO) PA guidelines for health promotion in adults establishes a weekly amount of 150–300 min of moderate intensity aerobic PA or at least 75–150 min of vigorous intensity aerobic PA, or an equivalent combination of both, which can be accrued at any PA domain (LTPA, CPA, at work, etc.) or a combination of PA domains.[11] This recommended PA amount should be complemented by reduced sedentary time. In terms of self-perceived effort, moderate PA is around 5 to 6 and vigorous PA is usually 7 to 8 on an individual's capacity scale of 0 (sitting) to 10 (maximal effort).[10] In practical terms, moderate PA can be performed while talking, without breaking into a sweat (a brisk walk, bicycling on flat terrain, swimming at a regular pace, etc.), while vigorous PA is marked by hyperventilation, difficulty talking, and transpiration (e.g., running, climbing stairs, fast bicycling, fast swimming, etc.).[10]

Therefore, this study aimed to further investigate the associations between PA in the LTPA, CPA, and combined LTPA + CPA domains under the WHO PA guidelines and migraine, exploring their relationships with migraine, especially with MA in the ELSA-Brasil cohort.

We hypothesized that meeting the WHO PA recommendations regardless of PA domain would be associated with a lower occurrence of both MO and MA, and lower migraine attack frequency. Exploring the associations between migraine, its subtypes, and PA patterns under the tenets of WHO recommendations for different PA domains and intensities may have clinical implications concerning PA recommendations for migraine management.

## METHODS

### Study design and population

This study is a secondary analysis of previously collected baseline data (2008–2010) of the ELSA-Brasil cohort.[11] Participants were recruited from a single public institution, the Sao Paulo Research Center, which was the only center with data on aura symptoms in the ELSA-Brasil cohort. The sample size was based on participants recruited from this center ($n = 5061$). The inclusion criteria were participants of both sex and active (regardless of the number of worked hours) or retired employees aged between 35 and 74 years. Exclusion criteria were current or recent pregnancy (<4 months before the interview), intention to quit the job soon, severe cognitive or communication impairment, and living outside of a study center's corresponding metropolitan area (for retired participants). Further details about the whole cohort are described elsewhere.[12] 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 were provided. This study complies with the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) guidelines for reporting data from observational research.

### Migraine diagnosis and migraine attack frequency—Outcome variables

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 Classification of Headache Disorders, 2nd edition (ICHD-2)[13] previously validated in Brazil.[14] For migraine diagnosis, the questionnaire showed a sensitivity of 90.2%, specificity of 57.9%, a positive predictive value of 65.7%, and a negative predictive value of 86.8% (Cohen's $\kappa = 0.47$).[14] The questionnaire investigates pain frequency, duration, quality, location, intensity, triggering factors, and accompanying symptoms, such as nausea or vomiting. For participants from the São Paulo Research Center, aura symptoms validation was performed, which included questions on visual, somatosensory, or motor symptoms based on ICHD-2.[13] Participants fulfilling the criteria for definite migraine without aura or probable migraine without aura were classified as "migraine without aura (MO)". Participants fulfilling the criteria for definite migraine with aura or probable migraine with aura were classified as the "migraine with aura (MA)" group. Participants experiencing no headache in the past 12 months were classified as the "no headache" group.

The data on migraine 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".

Baseline data on headache was collected onsite in the research center and detailed information about aura was inquired by the expert medical doctor from the ELSA-Brasil study by telephone.

## Physical activity classification—Exposure variable

The International Physical Activity Questionnaire (IPAQ) long-form was adopted to collect data on LTPA and CPA levels.[15] The IPAQ was previously translated and validated in Brazil.[16] The IPAQ has shown acceptable criterion validity, comparable to other self-report questionnaires ($r_{Spearman} = 0.30$), and very good reliability ($r_{Spearman} = 0.80$).[16] Compared to PA measured by accelerometer, the IPAQ showed strong validity for overall PA levels ($r_{Spearman} = 0.55$) and vigorous PA ($r_{Spearman} = 0.71$), but a weaker relationship for moderate PA ($r_{Spearman} = 0.21$).[15]

The IPAQ collects data regarding the PA levels over the prior 7 days. Within the LTPA domain, the IPAQ enquires about PA levels of moderate and vigorous PA related to recreation, sport, exercise, or leisure (e.g., "*During the last 7 days, on 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, on how many days did you walk to go from place to place?*). In the first wave of data collection in the ELSA-Brasil study, other PA domains and sitting time were not evaluated. The IPAQ long-form can be found on the website www.ipaq.ki.se.

The LTPA and CPA levels were analyzed separately and combined (LTPA + CPA). PA levels were computed by multiplying the weekly frequency (number of days) by the duration (min/day) of the PA performed. PA levels within each PA domain were categorized based on the WHO guidelines on PA for the adult's health.[11] Because the WHO guidelines accept that people should accumulate the recommended amount of PA regardless of the PA domain, we applied the same criteria for each PA domain.[11] As such, participants engaging in ≥150 min/week of moderate and/or ≥75 min/week of vigorous PA were set as "active", and those reporting <150 min/week of moderate or <75 min/week of vigorous PA were set as "somewhat active", and those not performing the minimum accountable amount of ≥10 min/week of PA were set as "inactive". The data on vigorous PA levels were only possible to retrieve from the LTPA domain, as the IPAQ does not inquire about vigorous PA intensity but only moderate PA intensity in the CPA domain.

## Covariates variables

Sociodemographic variables categories were sex, age (age range = 35–44, 45–54, 55–64, and 65–74 years), 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]), and marital status (Married, Separated, Single, Widow/Widower, or Other).

Depression and generalized anxiety disorder (GAD) were diagnosed based on the Clinical Interview Schedule-Revised (CIS-R) version adapted to Brazilian-Portuguese,[17] employed by trained interviewers from the ELSA-Brasil. The CIS-R assesses 14 symptoms 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. The cut-off for every symptom subscale considered clinically relevant is ≥2. Scores range from 0 to 4 for each subscale, except for depression ideas that ranges from 0 to 5. The relevant symptoms were grouped to determine the anxiety and depression diagnoses.

Cardiovascular comorbidities were hypertension, diabetes, dyslipidemia, metabolic syndrome, and obesity (body mass index ≥30 kg/m$^2$), and these variables were categorized as "yes" or "no". Data on blood pressure, fasting glycemia, total cholesterol and fractions (i.e., low-density lipoprotein, high-density lipoprotein), triglycerides, glycosylated hemoglobin, insulin, and homeostasis model assessment-insulin resistance (HOMA-IR) index obtained by standardized anthropometric techniques and laboratory, respectively, were used to build the diagnoses variables at baseline. Hypertension diagnosis was based on the previous clinical history and/or systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg and/or use of medication to treat hypertension. Diabetes was diagnosed based on the previous medical history of diabetes and/or use of medication to treat diabetes, and/or a fasting plasma glucose ≥126 mg/dl, and/or a 2-h plasma glucose ≥200 mg/dl, and/or a hemoglobin A1C (HbA1C) ≥6.5%. Dyslipidemia and metabolic syndrome diagnoses were defined according to National Cholesterol Program-Adult Treatment Panel III (NCEP ATP III) criteria.[18]

For migraine prophylactic medications use (yes/no), the American Academy of Neurology's guideline was used, and we

included medications with evidence level A and B.[19] Level A: antiseizure drugs (divalproex sodium, sodium valproate, topiramate), β-blockers (propranolol, metoprolol, timolol); Level B: antidepressants (amitriptyline, venlafaxine) and β-blockers (atenolol, nadolol).

## Statistical analysis

Descriptive statistics of sociodemographic, clinical, and PA data are reported as absolute values and percentages, means with standard deviation (±SD), or median with interquartile range (IQR). Comparisons between MA, MO, and no headaches subgroups were performed by chi-square test and one-way analysis of variance with fixed factors and Bonferroni's adjustments for variables with normal distribution, or Kruskal–Wallis test for variables that violate the assumption of normal distribution.

Depending on the variables' characteristics, multivariable multinomial or ordinal logistic regression models computed the association between migraine subtypes and PA levels. The outcomes (migraine subtypes) are reported using crude and adjusted odds ratios (ORs) and 95% confidence intervals (CIs). Separate logistic regression models were run for each PA domain (LTPA, CPA, and combined LTPA + CPA) and the moderate and vigorous LTPA levels. An ordinal regression model was performed for each PA domain to analyze the associations between PA levels and migraine attack frequency. In these later models, to deal with small sample sizes in higher attack frequency categories, both migraine subtypes, as well as the PA levels inactive and somewhat active were pooled together.

All the adjusted models were controlled for the effects of the confounder variables age, sex, household income, marital status, educational level, ethnicity, obesity, depression, GAD, hypertension, diabetes, dyslipidemia, metabolic syndrome, and use of migraine prophylactic medication.

In the main association analyses, two separate sensitivity analyses were conducted to deal with the probable migraine ($n = 648$) and retiree ($n = 357$) cases in the main association analyses. Thus, probable migraine and retiree cases were excluded. In these analyses, we used the same multivariable logistic regression models in the LTPA, CPA, and combined PA domains. Because CPA could be influenced by functional status (i.e., working vs. retired), retired participants were excluded from the association analyses between CPA and migraine subtypes.

For all tests, a two-tailed $p < 0.05$ was considered statistically significant. Statistics were computed by Statistical Package for the Social Sciences (SPSS) software (IBM SPSS Statistics for Windows, Version 24.0. IBM Corp., Armonk, NY, USA).

# RESULTS

Of 5061 participants from the Sao Paulo Research Center, 4717 participants responded with full information on headaches and PA levels. We excluded 1939 participants from the analyses because they fulfilled the criteria for other non-migraine headache types that were not targeted by this study (e.g., TTH, secondary headaches). Of these, there were seven participants with missing data on CPA levels (no headache: five; MO: one; MA: one), therefore, they were excluded from analyses. Therefore, the main analyses were based on the comparison between MA, MO, and no headache (reference group), comprising 2773 participants in total.

Overall, the study sample's mean (SD) age was 52.3 (9.1) years, 1556/2773 (56.1%) were women, 1579/2773 (56.9%) were White, and 1161/2773 (41.8%) had complete graduation. All participants were free of any health condition that could limit any PA participation as defined by the WHO.[11] We identified a few participants who might be unable to exercise ($n = 18$) due to functional limitations. However, because the current WHO PA guidelines are more inclusive and recognize that any form of PA counts,[11] we did not exclude these participants from our analysis. These participants did report PA participation, with some meeting PA levels even higher than the minimum recommended amount in their leisure time (i.e., ≥150 min/week).

Participants with MA were predominantly female, younger, had higher education levels, showed a higher frequency of GAD, used more prophylactic medications, and had lower PA levels in the LTPA and combined PA domains compared to the "no headache" group. Table 1 summarizes the data regarding sociodemographic and clinical characteristics and PA levels between groups.

In this study's sample, 1370/2773 (49.4%) participants had overall migraine, 480/2773 (17.3%) had MA, and 890/2773 (32.0%) had MO. Overall, the adjusted models showed that meeting the WHO PA guidelines in the LTPA domain was associated with reduced odds of MA (OR 0.72, 95% CI 0.53–0.96; $p = 0.030$) and MO (OR 0.71, 95% CI 0.56–0.90; $p = 0.005$) (Table 2). The crude models showed significant associations of CPA and LTPA + CPA domains with reduced odds of both MA and MO; however, there were no significant associations between PA levels in these domains with any migraine subtype after the adjustment for confounding variables (Table 2).

To further investigate the associations between CPA and migraine, we performed a logistic regression model with MA and MO pooled together as the outcome variable. In this analysis, being active in the CPA domain was associated with reduced odds of migraine in the crude (OR 0.78, 95% CI 0.64–0.95; $p = 0.015$), but not in the adjusted (OR 0.99, 95% CI 0.77–1.27; $p = 0.942$) model.

Table 3 shows the crude and adjusted odds of LTPA stratified by intensity. The adjusted regression analyses showed that meeting the WHO PA guidelines within moderate intensity was associated with reduced odds of MA (OR 0.56, 95% CI 0.320–0.99; $p = 0.049$), while both active (OR 0.55, 95% CI 0.395–0.77; $p = 0.001$) and somewhat active (OR 0.71, 95% CI 0.51–0.99; $p = 0.045$) within vigorous PA intensity were associated with reduced odds of MO (Figure 1).

Regarding migraine attack frequency, the adjusted ordinal regression models showed that, compared to the lowest migraine attack level ("once in a while"), participants with migraine who met the WHO PA guidelines in the LTPA (OR 4.11, 95% CI 1.26–13.3; $p = 0.019$) and CPA domains (OR 3.69, 95% CI 1.26–10.7; $p = 0.017$)

**TABLE 1** Baseline characteristics and physical activity pattern of 2773 participants from the ELSA-Brasil study

| Characteristic | No headache (*n* = 1403) | MO (*n* = 890) | MA (*n* = 480) |
|---|---|---|---|
| Age, years, median (IQR) | 55 (49–62) | 49 (44–55)* | 47 (43–53)*,† |
| Age range, *n* (%) | | | |
| 35–44 | 171 (12.1) | 242 (27.2)[a] | 154 (30.1)[a] |
| 45–54 | 462 (32.9) | 417 (46.9)[a] | 226 (47.1)[a] |
| 55–64 | 499 (35.6) | 188 (21.1)[a] | 90 (18.8)[a] |
| 65–74 | 271 (19.3) | 43 (4.8)[a] | 10 (2.1)[a] |
| Sex, *n* (%) | | | |
| Female | 518 (36.9) | 653 (73.4)[a] | 385 (80.2)[a,b] |
| Male | 885 (63.1) | 237 (26.6)[a] | 95 (19.8)[a,b] |
| Ethnicity—Self-reported, *n* (%) | | | |
| Black | 200 (14.6) | 131 (14.9) | 73 (15.2) |
| Brown | 275 (20.1) | 212 (24.1) | 115 (24.0) |
| White | 807 (58.9) | 499 (56.8) | 273 (57.1) |
| Others (Asian, indigenous, or native) | 89 (6.5) | 37 (4.2) | 17 (3.5) |
| Education, *n* (%) | | | |
| Elementary | 302 (21.6) | 122 (13.8)[a] | 60 (12.5)[a] |
| High School | 480 (34.2) | 394 (44.2)[a] | 255 (53.0)[a] |
| College | 622 (44.2) | 374 (42.0) | 165 (34.5)[a,b] |
| Household income[§], *n* (%) | | | |
| <US$1245 | 445 (31.8) | 285 (32.2) | 175 (36.4) |
| US$1245–3319 | 498 (35.6) | 428 (48.1) [a] | 230 (48.0)[a] |
| >US$3319 | 455 (32.6) | 175 (19.7) [a] | 75 (15.6)[a] |
| Marital status, *n* (%) | | | |
| Married | 953 (67.8) | 595 (66.9) | 301 (62.8) |
| Separated | 202 (14.4) | 121 (13.6) | 90 (18.7) |
| Single | 158 (11.2) | 100 (11.2) | 51 (10.6) |
| Widow/widower | 60 (4.3) | 50 (5.6) | 23 (4.8) |
| Other | 32 (2.3) | 24 (2.7) | 15 (3.1) |
| Comorbidities and clinical data | | | |
| BMI, kg/m$^2$, median (IQR) | 27.1 (24.2–30.2) | 26.6 (23.7–30.1) | 27.4 (24.3–30.6) |
| Obesity, *n* (%) | 378 (27.5) | 230 (26.0) | 143 (30.2) |
| Hypertension, *n* (%) | 548 (39.1) | 248 (27.9)[a] | 136 (28.3)[a] |
| Diabetes, *n* (%) | 367 (26.1) | 175 (19.6)[a] | 77 (16.0)[a] |
| Dyslipidemia, *n* (%) | 909 (64.8) | 556 (62.6) | 289 (60.2) |
| Metabolic syndrome, *n* (%) | 183 (13) | 85 (9.5) | 46 (9.6) |
| Depression, *n* (%) | 57 (2.9) | 58 (6.5)[a] | 58 (12.1)[a] |
| Generalized anxiety disorder (%) | 85 (6.1) | 165 (19.1)[a] | 138 (29.3)[a,b] |
| Migraine preventive medication, *n* (%) | 69 (4.9) | 62 (7.0) | 51 (10.6)[a] |
| Migraine frequency, *n* (%) | | | |
| Once in a while | – | 377 (42.4) | 140 (29.1)[b] |
| 1–2 times/month | – | 241 (27.1) | 131 (27.2) |
| Once a week | – | 83 (9.3) | 62 (12.9) |
| More than once a week | – | 150 (16.9) | 108 (22.5)[b] |
| Daily | – | 38 (4.3) | 40 (8.3)[b] |

(Continues)

TABLE 1 (Continued)

| Characteristic | No headache (*n* = 1403) | MO (*n* = 890) | MA (*n* = 480) |
|---|---|---|---|
| Physical activity pattern | | | |
| Level, *n* (%) | | | |
| LTPA | | | |
| Inactive | 879 (62.7) | 645 (72.5)[a] | 361 (75.2)[a] |
| Somewhat active | 172 (12.3) | 78 (8.8)[a] | 41 (8.5) |
| Active | 352 (25.0) | 167 (18.7)[a] | 78 (16.3)[a] |
| CPA | | | |
| Inactive | 335 (23.9) | 230 (25.8) | 131 (27.3) |
| Somewhat active | 541 (38.6) | 376 (42.2) | 192 (40) |
| Active | 527 (37.6) | 284 (31.9)[a] | 157 (32.7) |
| LTPA + CPA | | | |
| Inactive | 208 (14.8) | 159 (17.9) | 100 (20.8)[a] |
| Somewhat active | 439 (31.3) | 330 (37.1)[a] | 173 (36.0) |
| Active | 756 (53.9) | 401 (45.1)[a] | 207 (43.1)[a] |

*Note*: [§]All sources, including pension or retirement annuity. Generalized anxiety disorder and depression diagnoses were based on the Clinical Interview Schedule-Revised (CIS-R).[16] Hypertension was defined by systolic blood pressure >140 mmHg or diastolic blood pressure >90 mmHg, history of hypertension diagnosed by physician, or current treatment. Diabetes was defined as previous medical history of diabetes, use of medication to treat diabetes, a fasting plasma glucose >126 mg/dl, a 2-h plasma glucose >200 mg/dl, or an HbA1C >6.5%. Dyslipidemia was assessed according to the National Cholesterol Program-Adult Treatment Panel III (NCP-ATPIII) guidelines,[17] as follows: low-density lipoprotein cholesterol >130 mg/dl or use of lipid-lowering drug. Median test or one-way analysis of variance, Bonferroni-adjusted: $^{*}p < 0.01$ vs. No headache; $^{\dagger}p < 0.05$ vs. MO; chi-square test, Bonferroni-adjusted: $^{a}p < 0.05$ vs. No headache; $^{b}p < 0.05$ vs. MO.

Abbreviations: BMI, body mass index; CPA, commuting physical activity; IQR, interquartile range; LTPA, leisure-time physical activity; LTPA + CPA, combined LTPA and CPA levels; MA, migraine with aura; MO, migraine without aura.

were associated with higher odds of less frequent migraine attacks (1, 2 attacks/month), whereas there were reduced odds of daily migraine attacks for participants with migraine who met the WHO PA guidelines in the LTPA (OR 0.275, 95% CI 0.083–0.90; $p = 0.034$), CPA (OR 0.194, 95% CI 0.064–0.58; $p = 0.004$), and combined domains (OR 0.115, 95% CI 0.032–0.41; $p = 0.001$) (Table 4).

After sensitivity analyses, our main findings remained in the same direction. After the exclusion of probable migraine cases from the whole sample, the multivariable regression models showed that active people in the LTPA domain had reduced odds of MA (OR 0.68, 95% CI 0.50–0.94; $p = 0.019$) and MO (OR 0.45, 95% CI 0.319–0.70; $p < 0.001$). However, no further significant associations were found in the CPA and combined PA domains. After the exclusion of retiree from the main analyses, physically active people in the LTPA domain still showed significantly reduced odds of MO (OR 0.67, 95% CI 0.51–0.87; $p = 0.004$), but not for MA (OR 0.74, 95% CI 0.53–1.01; $p = 0.086$). There were still no significant associations between any PA levels in the CPA or combined domains with any migraine headaches after the exclusion of the retiree.

## DISCUSSION

This study brings novel information about the complex relationship between migraine subtypes and PA according to current public health guidelines. Our findings showed that meeting the WHO PA guidelines for LTPA, but not CPA or combined PA domains, is associated with reduced odds of migraine. LTPA showed distinct associations depending on aura symptoms and PA intensity. Meeting the WHO recommendations for moderate LTPA is associated with reduced MA, while vigorous LTPA is associated with reduced MO in leisure time. Compared to inactive people with migraine, meeting the WHO PA guidelines for all PA domains was associated with a lower likelihood of migraine chronification.

Our findings have similarities and discrepancies compared to the associations reported from the Danish Twin Registry study regarding aura symptoms and PA intensity.[3] In the Danish cohort, recreational PA of both intensities "heavy physical exercise" and "light physical exercise" were associated with reduced odds of MO, while only "heavy physical exercise" intensity was associated with reduced odds of MA. These findings diverge from ours, which showed that moderate PA is associated with reduced odds of MA. Conversely, in the Danish study men engaging in "heavy physical exercise" exhibited a lower likelihood of MO but not MA.[3] These later data concur with our study.

The discrepancies between the Danish study and the ELSA-Brasil study may be ascribed to several factors related to study methodology and samples' characteristics. For example, the PA questionnaire in the Danish study did not assess moderate PA as defined by the WHO. The ELSA-Brasil cohort is older than the Danish cohort (~10 years older). Furthermore, in this analysis, the ELSA-Brasil study included confounder variables that could affect PA behavior, such as psychiatric and cardiovascular comorbidities, and migraine preventive drugs, which were not controlled for in the Danish study.

**TABLE 2** Odds ratios (ORs) with 95% confidence intervals (CIs) for migraine headaches according to physical activity levels in 2773 participants from the ELSA-Brasil study

| | MO ($n$ = 890) | | MA ($n$ = 480) | |
|---|---|---|---|---|
| | OR (95% CI) | $p$ | OR (95% CI) | $p$ |
| LTPA—Crude | | | | |
| Inactive | Ref. (1.0) | | Ref. (1.0) | |
| Somewhat active | 0.73 (0.59–0.91) | 0.006 | 0.69 (0.52–0.90) | 0.004 |
| Active | 0.59 (0.49–0.72) | <0.001 | 0.48 (0.381–0.62) | <0.001 |
| LTPA—Adjusted | | | | |
| Inactive | Ref. (1.0) | | Ref. (1.0) | |
| Somewhat active | 0.83 (0.64–1.07) | 0.167 | 0.84 (0.61–1.15) | 0.284 |
| Active | 0.71 (0.56–0.90) | 0.005 | 0.72 (0.53–0.96) | 0.030 |
| CPA—Crude | | | | |
| Inactive | Ref. (1.0) | | Ref. (1.0) | |
| Somewhat active | 1.03 (0.83–0.28) | 0.751 | 0.91 (0.70–1.18) | 0.489 |
| Active | 0.79 (0.63–0.99) | 0.045 | 0.76 (0.58–1.01) | 0.051 |
| CPA—Adjusted | | | | |
| Inactive | Ref. (1.0) | | Ref. (1.0) | |
| Somewhat active | 1.23 (0.96–1.59) | 0.100 | 1.13 (0.83–1.54) | 0.432 |
| Active | 0.97 (0.74–1.27) | 0.835 | 0.94 (0.68–1.31) | 0.751 |
| LTPA + CPA—Crude | | | | |
| Inactive | Ref. (1.0) | | Ref. (1.0) | |
| Somewhat active | 0.91 (0.68–1.21) | 0.543 | 0.85 (0.61–1.20) | 0.371 |
| Active | 0.61 (0.47–0.80) | <0.001 | 0.52 (0.388–0.71) | <0.001 |
| LTPA + CPA—Adjusted | | | | |
| Inactive | Ref. (1.0) | | Ref. (1.0) | |
| Somewhat active | 1.13 (0.76–1.68) | 0.532 | 1.15 (0.82–1.60) | 0.414 |
| Active | 0.82 (0.57–1.18) | 0.294 | 0.83 (0.61–1.13) | 0.256 |

*Note*: Reference group: No headaches ($n$ = 1403). The adjusted models were controlled for the effects of confounder variables age, sex, household income, marital status, educational level, and ethnicity, obesity depression, generalized anxiety disorder, hypertension, diabetes, dyslipidemia, metabolic syndrome, and use of migraine prophylaxis.

Abbreviations: CPA, commuting physical activity; LTPA, leisure-time physical activity; MA, migraine with aura; MO, migraine without aura.

The associations observed here regarding PA intensity are akin to data from clinical studies evaluating the effects of aerobic exercise interventions for migraine prevention.[20–23] Moderate- and high-intensity (i.e., vigorous) aerobic exercise has been shown effective to reduce migraine clinical outcomes,[20–23] with evidence of superior therapeutic effects of vigorous over moderate aerobic exercise.[21,22] However, further studies comparing the effect of interventions with different exercise intensities on MA are needed to confirm these findings.

The relationship between PA in the commuting time and migraine disorders has never been studied. The CPA assessed by the IPAQ refers to walking and/or bicycling in the transport to/from work or while doing errands. Here, we found a higher proportion of participants in all groups who met the WHO PA guidelines in the CPA domain compared to the LTPA domain. However, CPA was not associated with significant changes in migraine occurrence. The explanations for these findings may lie in the possible detrimental effects of CPA on migraine in combination with other social and environmental factors, such as air pollution, whether it is performed voluntarily or forced, and associated with occupation type, which could outweigh the benefits of PA in other contexts (e.g., in the leisure time).

Air pollution exposure has been associated with both migraine attack frequency[24] and prevalence.[25] In the region where this study's cohort lives (i.e., the São Paulo metropolitan area), the spatial distribution of traffic air pollutants indicates a higher air pollution concentration in areas where bicycle lanes are built, as well as other urban walking connections, colocalizes with high vehicle traffic volume.[26] This would render active commuters more exposed to traffic-related pollutants. On the other hand, LTPA is usually performed at parks, indoor facilities (gyms, health clubs), or areas with calmer neighborhoods and more green spaces, which presumably may offer more protection against air pollutants. Hypothetically, higher exposure to pollutants during the commuting time could outweigh the benefits

**TABLE 3** Odds ratios (ORs) with 95% confidence intervals (CIs) for migraine headaches according to LTPA intensity in 2773 participants from the ELSA-Brasil study

| | MO ($n = 890$) | | MA ($n = 480$) | |
|---|---|---|---|---|
| | OR (95% CI) | *p* | OR (95% CI) | *p* |
| Moderate—Crude | | | | |
| Inactive | Ref. (1.0) | | Ref. (1.0) | |
| Somewhat active | 0.65 (0.50–0.84) | 0.001 | 0.58 (0.42–0.82) | 0.002 |
| Active | 0.86 (0.62–1.21) | 0.412 | 0.48 (0.286–0.80) | 0.005 |
| Moderate—Adjusted | | | | |
| Inactive | Ref. (1.0) | | Ref. (1.0) | |
| Somewhat active | 0.69 (0.51–0.94) | 0.020 | 0.73 (0.49–1.08) | 0.124 |
| Active | 0.93 (0.62–1.37) | 0.717 | 0.56 (0.320–0.99) | 0.049 |
| Vigorous—Crude | | | | |
| Inactive | Ref. (1.0) | | Ref. (1.0) | |
| Somewhat active | 0.72 (0.54–0.96) | 0.025 | 0.62 (0.43–0.90) | 0.013 |
| Active | 0.53 (0.40–0.71) | <0.001 | 0.50 (0.35–0.73) | <0.001 |
| Vigorous—Adjusted | | | | |
| Inactive | Ref. (1.0) | | Ref. (1.0) | |
| Somewhat active | 0.71 (0.51–0.99) | 0.045 | 0.81 (0.53–1.24) | 0.344 |
| Active | 0.55 (0.395–0.77) | 0.001 | 0.67 (0.44–1.03) | 0.072 |

*Note*: Reference group: No headaches ($n = 1403$). The adjusted models were controlled for the effects of confounder variables sex, age, household income, marital status, educational level, and ethnicity, obesity depression, generalized anxiety disorder, hypertension, diabetes, dyslipidemia, metabolic syndrome, and use of migraine prophylaxis.

Abbreviations: LTPA, leisure-time physical activity; MA, migraine with aura; MO, migraine without aura.

of PA on migraine. Agreeably, CPA has been associated with other unfavorable outcomes such as hypertension in women in the ELSA-Brasil cohort.[27]

As a physiological stress stimulus, the physical effort can be interpreted either as a "positive stressor" or "negative stressor" stimulus depending on the context and if it is a voluntary or forced stimulus. Unlike LTPA, CPA may not always represent a voluntary activity. Considering the social and geographic context of this cohort (e.g., large metropolitan area), CPA could be associated with the public transport characteristics, e.g., having to walk large distances between multiple bus/train terminals connections and bus/train stops and home. The translational literature has long indicated that voluntary and forced exercise may differentially affect brain and behavior, with very heterogeneous neurohumoral responses, including neurotransmitter systems related to perceived stress and pain processing, such as the monoamines, which are also related to migraine pathophysiology.[28] Thus, PA in the context of commuting time, i.e., CPA, for people with migraine might yield unfavorable clinical responses, e.g., representing an additional psychophysiological stress stimulus in their daily routine, especially for women with a heavier job and household-related strains. Agreeably, in the ELSA-Brasil cohort, job strain is associated with higher odds of migraine, with stronger associations in women.[29]

The lack of association between CPA and migraine subtypes in the fully adjusted models could also stem from a lack of power due to the small sample in the MA group. However, this pattern remained in the analysis with MA and MO groups pooled together, confirming a null association of CPA with migraine.

Interestingly, the evaluation of PA in a multidimensional domain, which has been encouraged by the WHO guidelines to account for the accumulated effects of PA on health outcomes,[11] showed no significant associations with migraine in women. Possibly, the null or negative associations of CPA may have balanced the positive effects of LTPA on reducing migraine occurrence, resulting in a lack of associations when they were combined into a multidimensional domain.

Moreover, all PA domains reduced the odds of daily migraine attacks in the fully adjusted model, suggesting that an active lifestyle, at least in the leisure time and commuting time, may be associated with reduced odds of migraine chronification. Nevertheless, this finding may be interpreted with caution, considering reverse causation as well. That is, people could be more active because they have fewer migraine attacks.

Collectively, based on the available data and the findings in this study, clinicians and healthcare professionals should encourage patients with migraine to focus on PA in their leisure time. From a practical perspective, vigorous PA is performed in shorter duration sessions to comply with the recommended amount of 75 min/week (e.g., 15–20 min/session, 4–5 times/week) could be prioritized for people with migraine in general, while people with MA should be advised to prioritize moderate PA, accumulating a weekly amount of 150 min.

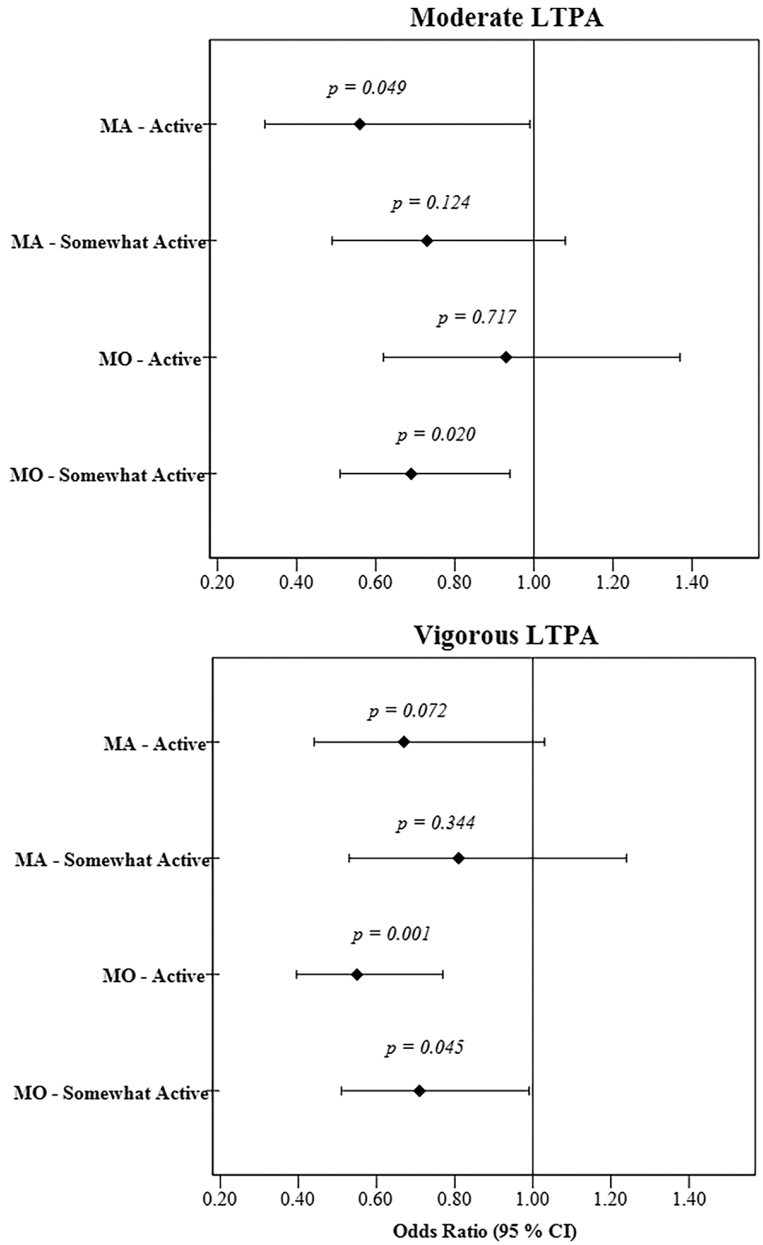


**FIGURE 1** Odds ratio (ORs) with 95% confidence intervals (CIs) for migraine subtypes according to leisure-time physical activity (LTPA) intensity in 2780 participants from the ELSA-Brasil study; Reference group: No headaches; LTPA reference level: Inactive; the adjusted models were controlled for the effects of confounder variables sex, age, household income, marital status, educational level, and ethnicity, obesity depression, generalized anxiety disorder, hypertension, diabetes, dyslipidemia, metabolic syndrome, and use of migraine prophylaxis. MA, migraine with aura MO, migraine without aura.

Additionally, the lower likelihood of MO in participants engaging in vigorous PA in their leisure time, even below the minimum amount of 75 min/week, may suggest that this population could also benefit from the trending PA modalities involving exercises of short durations and higher intensities (e.g., the "7-min Workout"), which fit the current WHO PA guidelines and are also endorsed by the American College of Sports Medicine.[30] Nevertheless, more studies based on randomized control trials testing the effect of interventions adopting different PA intensity and modalities, or cohort's prospective data with objective measurements of PA levels, are necessary to substantiate clinical recommendations.

The associations of PA with migraine subtypes could be partly explained by their pathophysiological features. Migraine, especially MA, has been linked to abnormal musculoskeletal and brain energy metabolism and mitochondrial disfunction,[31–34] neuroinflammation,[35] and right-to-left shunt caused by a patent foramen ovale.[36,37] All these pathophysiological mechanisms could be either related to exercise-triggered migraine (and aura) attacks[38,39] or be targeted by the preventive effects of regular PA.[20–23,40] The adherence to a PA regime with both moderate or vigorous PA as recommended by the WHO could mediate the preventive, antimigraine (or anti-aura) effects through improved mitochondrial function,[20] as well as by

**TABLE 4** Odds ratios (ORs) with 95% confidence intervals (CIs) for migraine attacks frequency according to PA levels categories in the LTPA, CPA, and combined LTPA + CPA domains in participants with migraine ($n = 1370$)

| | 1–2×/month ($n = 372$) | | 1×/week ($n = 145$) | | More than once/week ($n = 258$) | | Daily ($n = 78$) | |
|---|---|---|---|---|---|---|---|---|
| | OR (95% CI) | *p* | OR (95% CI) | *p* | OR (95% CI) | *p* | OR (95% CI) | *p* |
| LTPA—Crude model | | | | | | | | |
| Inactive/somewhat active | Reference (1.0) | | Reference (1.0) | | Reference (1.0) | | Reference (1.0) | |
| Active | 1.03 (0.94–1.13) | 0.463 | 0.45 (0.41–0.51) | <0.001 | 0.308 (0.271–0.351) | <0.001 | 0.073 (0.057–0.092) | <0.001 |
| LTPA—Adjusted model | | | | | | | | |
| Inactive/somewhat active | Reference (1.0) | | Reference (1.0) | | Reference (1.0) | | Reference (1.0) | |
| Active | 4.11 (1.26–13.3) | 0.019 | 1.75 (0.54–5.69) | 0.349 | 1.18 (0.36–3.86) | 0.774 | 0.275 (0.083–0.90) | 0.034 |
| CPA—Crude model | | | | | | | | |
| Inactive/somewhat active | Reference (1.0) | | Reference (1.0) | | Reference (1.0) | | Reference (1.0) | |
| Active | 1.04 (0.91–1.19) | 0.549 | 0.46 (0.40–0.54) | <0.001 | 0.296 (0.250–0.352) | <0.001 | 0.056 (0.040–0.077) | <0.001 |
| CPA—Adjusted model | | | | | | | | |
| Inactive/somewhat active | Reference (1.0) | | Reference (1.0) | | Reference (1.0) | | Reference (1.0) | |
| Active | 3.69 (1.26–10.7) | 0.017 | 1.63 (0.55–4.75) | 0.371 | 1.03 (0.353–3.02) | 0.953 | 0.194 (0.064–0.58) | 0.004 |
| LTPA + CPA—Crude model | | | | | | | | |
| Inactive/somewhat active | Reference (1.0) | | Reference (1.0) | | Reference (1.0) | | Reference (1.0) | |
| Active | 1.14 (0.97–1.35) | 0.103 | 0.51 (0.42–0.61) | <0.001 | 0.326 (0.269–0.395) | <0.001 | 0.065 (0.048–0.089) | <0.001 |
| LTPA + CPA—Adjusted model | | | | | | | | |
| Inactive/somewhat active | Reference (1.0) | | Reference (1.0) | | Reference (1.0) | | Reference (1.0) | |
| Active | 2.05 (0.58–7.20) | 0.259 | 0.88 (0.252–3.08) | 0.843 | 0.57 (0.163–2.00) | 0.381 | 0.115 (0.032–0.41) | 0.001 |

*Note*: The migraine with aura and migraine without aura groups are pooled together. Reference group: "Once in a while" ($n = 517$); the adjusted models were controlled for the effects of confounder variables sex, age, household income, marital status, educational level, and ethnicity, obesity depression, generalized anxiety disorder, hypertension, diabetes, dyslipidemia, metabolic syndrome, and use of migraine prophylaxis.

Abbreviations: CPA, commuting physical activity; LTPA, leisure-time physical activity.

stimulating anti-inflammatory/anti-nociceptive[21] and cardiorespiratory mechanisms.[20,22,23]

Finally, psychological/behavioral factors could be involved in the intensity-specific association of PA with migraine subtypes. As physical exercise is considered a migraine trigger and prolonged or strenuous exercise can trigger MA attacks,[38,39,41] people with MA could perceive/believe that vigorous PA would precipitate/worsen migraine attacks, which would make them more prone to engage preferably in moderate PA in the leisure time.

## Strengths and limitations

This study presents strengths worth mentioning. We collected the headache data through interviews employing a validated questionnaire, based on International Headache Society criteria. PA levels and domains were based on standardized measures and definitions according to the current WHO PA guidelines. Also, we controlled confounding variables that could influence the relationship between PA and migraine, such as age, psychiatric and cardiovascular comorbidities, and migraine preventive medication.

The generalizability of this study is limited by the sociodemographic characteristics of the ELSA-Brasil cohort, which have higher income and educational attainment compared to the Brazilian general population. Yet, the social and ethnic diversity of the cohort is still like those of people living in large cities in Brazil.[42] This suggests that our external validity may extend to large urban areas.

Agreeably, there are several similarities in the prevalence of selected behavioral risk factors and chronic conditions between ELSA-Brasil and larger surveys, such as the Surveillance System of Risk and Protection Factors for Chronic Diseases by Telephone Survey (VIGITEL).[43] Another limitation is recall bias from PA data retrieved from a questionnaire, which may result in inaccurate PA levels estimates. Evidence from studies comparing PA levels assessed by IPAQ or accelerometry indicates that IPAQ may

overestimate vigorous and underestimate moderate PA levels.[15] Moreover, the cross-sessional design of the present study performed in the ELSA-Brasil makes it difficult to establish causality between variables of interest evaluated. Finally, the IPAQ was designed for populations aged 18–65 years, and 11.7% of the sample in this study was aged >65 years. However, the IPAQ has still shown moderate/acceptable validity in elderly populations in Brazil and abroad.[44,45]

## CONCLUSION

In summary, meeting the current WHO PA recommendations in the leisure time but not during the commuting time reduces the odds of migraine, with specific associations depending on the presence of aura symptoms and PA intensity. Meeting the WHO recommendations for moderate PA is associated with reduced MA, while vigorous PA is associated with reduced MO in leisure time.

Future analyses involving prospective data and other PA modalities and domains could help to better understand the relationship between PA in different domains and migraine. These data might have some impact on public health, as it has fundamentals for the development of migraine-specific PA guidelines to reduce migraine headaches prevalence and burden. A second wave collecting longitudinal data on headache is being conducted to further explore these associations in the ELSA-Brasil cohort.

### AUTHOR CONTRIBUTIONS

*Study concept and design*: Arão Belitardo Oliveira, Alessandra C. Goulart, Mario Fernando Prieto Peres. *Acquisition of data*: Alessandra C. Goulart, Isabela M. Benseñor, Paulo A. Lotufo. *Analysis and interpretation of data*: Arão Belitardo Oliveira, Alessandra C. Goulart, Isabela M. Benseñor, Mario Fernando Prieto Peres. *Drafting of the manuscript*: Arão Belitardo Oliveira, Alessandra C. Goulart, Isabela M. Benseñor, Mario Fernando Prieto Peres. *Revising it for intellectual content*: Arão Belitardo Oliveira, Alessandra C. Goulart, Isabela M. Benseñor, Mario Fernando Prieto Peres, Juliane Prieto Peres Mercante, Maria del Carmen B. Molina, Paulo A. Lotufo. *Final approval of the completed manuscript*: Arão Belitardo Oliveira, Alessandra C. Goulart, Isabela M. Benseñor, Mario Fernando Prieto Peres, Juliane Prieto Peres Mercante, Maria del Carmen B. Molina, Paulo A. Lotufo.

### CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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