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Does physical activity and inflammation mediate the job stress-headache relationship? A sequential mediation analysis in the ELSA-Brasil study

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ABSTRACT

Background: Evidence indicates that physical activity reduces stress and promote a myriad of health-enhancing effects through anti-inflammatory mechanisms. However, it is unknown whether these mechanisms interfere in the association between psychosocial job stress and headache disorders.
Objective: To test whether physical activity and its interplay with the systemic inflammation biomarkers high-sensitivity C-reactive protein (hs-CRP) and acute phase glycoproteins (GlycA) would mediate the associations between job stress and headache disorders.
Methods: We cross-sectionally evaluated the baseline data from the Brazilian Longitudinal Study of Adult Health (ELSA-Brasil) regarding job stress (higher demand and lower control and support subscales), migraine and tension-type headache (ICHD-2 criteria), self-reported leisure-time physical activity, and plasma hs-CRP and GlycA levels. Conditional process analyses with a sequential mediation approach were employed to compute path coefficients and 95 % confidence intervals (CI) around the indirect effects of physical activity and biomarkers on the job stress-headache relationship. Separate models were adjusted for sex, age, and depression and anxiety. Further adjustments added BMI smoking status, and socioeconomic factors.
Results: In total, 7,644 people were included in the study. The 1-year prevalence of migraine and tension-type headache were 13.1 % and 49.4 %, respectively. In models adjusted for sex, age, anxiety, and depression, the association between job stress (lower job control) and migraine was mediated by physical activity [effect = −0.039 (95 %CI: −0.074, −0.010)] but not hs-CRP or GlycA. TTH was associated with higher job control and lower job demand, which was mediated by the inverse associations between physical activity and GlycA [Job Control: effect = 0.0005 (95 %CI: 0.0001, 0.0010); Job Demand: effect = 0.0003 (95 %CI: 0.0001, 0.0007]. Only the mediating effect of physical activity in the job stress-migraine link remained after further adjustments including socioeconomic factors, BMI, smoking, and the exclusion of major chronic diseases.
Conclusion: In the ELSA-Brasil study, physical activity reversed the link between job stress and migraine independently of systemic inflammation, while the LTPA-mediated downregulation of GlycA was associated with lower job stress-related TTH.

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1. Introduction

Migraine and tension-type headache (TTH) are the most prevalent brain disorders globally (Stovner et al., 2018). Their prevalence peaks during the most productive years of population's professional life, causing a considerable personal impact and enormous socioeconomic toll on societies (Linde et al., 2012; Oliveira et al., 2020; Yu et al., 2012). In Brazil, the 1-year prevalence of migraine and TTH have been estimated to be 15.8 % and 29.5 % of the population, respectively (Queiroz and Junior, 2015).

Headache disorders exhibit bi-directional relationships with environmental and behavioral factors such as emotional stress (Stubberud et al., 2021) and physical activity (Bond et al., 2015; Oliveira et al., 2021). Psychosocial job stress has been related to higher headache attacks (Urhammer et al., 2020), migraine occurrence or prevalence (Leineweber et al., 2020; Santos et al., 2014), and migraine incidence in women (Mäki et al., 2008). Leisure-time physical activity (LTPA) levels are inversely associated with headache attack frequency and migraine occurrence and prevalence (Hagen et al., 2018; Oliveira et al., 2022; 2021), while daily step counts are inversely associated with migraine incidence (Master et al., 2022).

From a pathophysiological viewpoint, primary headache disorders are characterized by a multifaceted nature, which also includes the participation of pro-inflammatory immune mediators (Thuraiaiyah et al., 2022). Observational studies has reported several cytokines involved with people with headache disorders, mostly migraine (Bø et al., 2009; Oliveira et al., 2017a; Thuraiaiyah et al., 2022). Preclinical migraine animal models suggest the involvement of mast cell degranulation-derived inflammatory mediators (Bhatt et al., 2014; Levy et al., 2012; 2007), while a review of clinical studies have found higher high-sensitivity C-reactive protein (hs-CRP) in migraine patients compare to counterparts without headache (Lippi et al., 2014). A

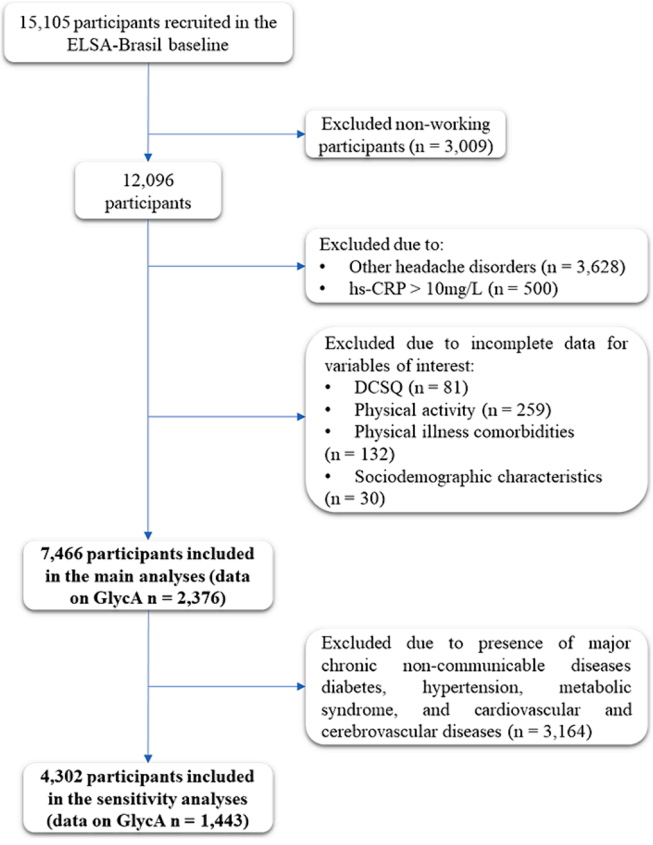

Fig. 1. Participants' flow in the study.

Table 1
Sociodemographic and clinical characteristics of 7,466 current workers in the ELSA-Brasil cohort at baseline.

	Groups		
	No Headache (n = 2,789)	TTH (n = 3,692)	Migraine (n = 985)
Age, years, mean (95 % CI)	51.4 (51.2–51.7)	48.6 (48.3–48.8) [c]	47.3 (46.9–47.7) [c,f]
BMI, kg/m^2, mean (95 % CI)	26.9 (26.7–27.1)	26.7 (26.5–26.8)) [a]	26.4 (26.1–26.7)
Gender, n (%)			
Female	881 (31.6)	1,676 (45.4) *	850 (86.3) *, #
Ethnicity – self-reported, n (%)			
White	1,292 (46.3)	2,006 (54.3) *	485 (49.2) #
Brown	868 (31.1)	1,033 (28.0) *	273 (27.79) #
Black	514 (18.4)	534 (14.5)	193 (19.6)
Other (yellow, indigenous, or native)	115 (4.1)	119 (3.2)	34 (3.5)
Education, n (%)			
Primary	447 (16.0)	326 (8.8) *	76 (7.7) *
High School	1,015 (36.4)	1,201 (32.5) *	410 (41.6) *, #
College	1,327 (47.6)	2,165 (58.6) *	499 (50.7) #
Household Income, n (%)			
<US$1245	870 (31.2)	857 (23.2) *	296 (30.1) #
US$1245–3319	1,159 (41.6)	1,641 (44.4) *	474 (48.1) *, #
>US$3,319	760 (27.2)	1,194 (32.3) *	215 (21.8) *, #
Marital Status, n (%)			
Married	1,953 (70.0)	2,576 (69.8)	597 (60.6) *, #
Separated	422 (15.1)	538 (14.6)	181 (18.4) *, #
Single	255 (9.1)	355 (9.6)	138 (14.0) *, #
Widower	78 (2.8)	93 2.5)	33 (3.4)
Other	81 (2.9)	130 (3.5)	36 (3.7)
Mental Health Disorder, n (%)			
Depression	62 (2.2)	84 (2.3) *	93 (9.4) *, #
GAD	207 (7.4)	376 (10.2) *	260 (26.4) *, #
Cardiometabolic Comorbidities, n (%)			
Cardiovascular Diseases	182 (6.5)	196 (5.3) *	67 (6.8)
Hypertension	1,015 (36.4)	1,102 (29.8) *	218 (22.1) *, #
Diabetes	616 (22.1)	548 (14.8) *	110 (11.2) *, #
Dyslipidaemia	1,784 (64.0)	2,246 (60.8) *	581 (59.0) *
Metabolic Syndrome	273 (9.8)	290 (7.9) *	107 (10.9)
Lifestyle Factors			
Current Smoker, n (%)	428 (15.3)	453 (12.3) *	142 (14.4)
LTPA (min.week^{-1}), mean (95 % CI)	147.3 (139.6–154.9)	135.7 (129.6–141.8) [a]	99.4 (89.2–109.5) [c, f]
Log LTPA, mean (95 % CI)	2.26 (2.24–2.28)	2.23 (2.22–2.25)	2.22 (2.17–2.23) [b]
Inflammation Biomarkers			
Plasma hs-CRP (mg/L), mean (95 % CI)	2.13 (2.0–2.19)	2.10 (2.02–2.15)	2.34 (2.20–2.48) [a, e]
Log hs-CRP, mean (95 % CI)	0.12 (0.10–0.14)	0.11 (0.09–0.12)	0.15 (0.11–0.17)
Low-grade chronic inflammation, n (%) [§]	661 (23.7)	860 (23.3)	280 (28.4) *, #
Plasma GlycA (μmol/L), mean (95 % CI) [§§]	410.8 (406.4–415.1)	403.7 (400.2–407.1) [a]	416.0 (409.1–422.8) [e]
DCSQ Scores, mean (95 % CI) [‡]			
DCSQ Demand (5–20)	15.10 (15.01–15.19)	15.20 (15.13–15.28)	15.56 (15.41–15.70) [c, f]
Log DCSQ Demand	1.17 (1.17–1.17)	1.17 (1.17–1.17)	1.18 (1.18–1.19) [c]
DCSQ Control (6–24)	17.95 (17.84–18.07)	18.14 (18.04–18.23) [a]	17.39 (17.21–17.57) [c, f]
Log DCSQ Control	1.24 (1.24–1.25)	1.25 (1.24–1.25) [a]	1.23 (1.22–1.23) [c, f]

(continued on next page)

Table 1 (*continued*)

	Groups		
	No Headache (n = 2,789)	TTH (n = 3,692)	Migraine (n = 985)
DCSQ Support (6–24)	20.16 (20.04–20.28)	19.83 (19.73–19.93) [c]	19.14 (18.93–19.36) [c, f]
Log DCSQ Support	1.29 (1.29–1.30)	1.29 (1.28–1.29) [b]	1.27 (1.26–1.27) [c, f]
Karaseḱs job strain model, n (%)			
Low-strain job	613 (22.0)	860 (23.3)	151 (15.3) [*, #]
Passive job	879 (31.5)	1,055 (28.6) [*]	290(29.4) [*]
Active job	660 (23.7)	916 (24.8)	255 (25.9)
High-strain job	637 (22.8)	861 (23.3)	289 (29.3) [*, #]

TTH: Tension-type headache; CI: Confidence Interval; hs-CRP: High-sensitivity C-reactive protein; [a]: p-value < 0.05, [b]: p-value < 0.01, [c]: p-value < 0.001 *vs* No Headache, and [d]: p-value < 0.05, [e]: p-value < 0.01, [f]: p-value < 0.001 *vs* TTH, One-way ANOVÁs pairwise comparison with Bonferroni adjustment; *: p-value < 0.05 *vs* No Headache, and #: p-value < 0.05 *vs* TTH, Chi-square test, Bonferroni adjusted; GAD: Generalized Anxiety Disorder LTPA: Leisure-time physical activity; CPA: Commuting physical activity. §: Defined as having hs-CRP plasma concentration ≥ 3.0 mg/L. §§: Sample size for GlycA analysis = 2,376 (no headache: n = 863; TTH: n = 1,151; Migraine: n = 362). ‡: DCSQ scores are inverted from original score values; thus, the higher the score the higher the "stress" level in the demand subscale, while the lower the score the higher the "stress" level in the control and support subscale (lower control or lower support).

prospective, population-based study showed that hs-CRP, a well-recognizable biomarker of low-grade chronic inflammation, has also been associated with an increased risk of migraine in the general population (Hagen et al., 2020).

Elevated hs-CRP levels have been proposed as a potential underlying mechanism through which psychosocial job stress contributes to both physical and mental illness (Christensen et al., 2021; Duchaine et al., 2021; Eguchi et al., 2016; Furman et al., 2019; Xu et al., 2015). On the other hand, LTPA (mostly aerobic exercise) promotes stress-buffering and anti-inflammatory effects by reducing hs-CRP levels (Del Rosso et al., 2023; Fedewa et al., 2017; Hammonds et al., 2016; Papagianni et al., 2023; Ploeger et al., 2009; Queiroz et al., 2020). Also, there is abundant evidence linking psychosocial job stress and physical inactivity with low-grade chronic inflammation (higher hs-CRP levels) in working populations (Duchaine et al., 2021; Furman et al., 2019; Xu et al., 2015).

The anti-inflammatory effects of LTPA are considered a contributing mechanism through which exercise and cardiorespiratory fitness can prevent chronic diseases and reduce mortality Abelhad et al., 2023; Lavie et al., 2019; Popovic and Lavie, 2023), and mitigate several forms of psychosocial stress (Furman et al., 2019; Molina-Hidalgo et al., 2023; Popovic et al., 2022; Popovic and Lavie, 2023; Simpson et al., 2021; Wang et al., 2023)' including job stress (Emeny et al., 2012).

While hs-CRP is the most studied systemic inflammation biomarker in the context of the health-enhancing effects of regular LTPA (Del Rosso et al., 2023; Fedewa et al., 2017; Hammonds et al., 2016; Papagianni et al., 2023; Ploeger et al., 2009; Queiroz et al., 2020), more recently, acute phase glycoproteins (GlycA) has emerged as another exercise-induced anti-inflammatory biomarker (Barber et al., 2018). GlycA are a1-acid glycoprotein, haptoglobin, a1-antitrypsin, a1-antichymotrypsin, and transferrin reactants detected by nuclear magnetic resonance (Connelly et al., 2017). GlycA shows established inflammatory states, as glycosylation involves protein folding and stabilization, cellular adhesion, antigen recognition, and cell signaling (Connelly et al., 2017). As such, GlycA has been associated with several chronic inflammatory and cardiovascular diseases (Mehta et al., 2020), cardiovascular risk factors (Connelly et al., 2017; Tebar et al., 2023), metabolic diseases (Bartlett et al., 2017), and mental illness (Brunoni et al., 2020). GlycA has never been studies in the context of primary headache disorders.

Moreover, it is unknown whether psychosocial job stress, LTPA, and systemic inflammation biomarkers independently influence headache disorders or whether the job stress-headache relationship would be influenced by the inverse association between physical activity and systemic inflammation. Given the complex and multifaceted interplay between psychosocial job stress, physical and mental illness, and biomarkers of systemic chronic inflammation (Christensen et al., 2021; Duchaine et al., 2021; Eguchi et al., 2016; Furman et al., 2019; Xu et al., 2015), we wondered whether the link between job stress and headache disorders would be influenced by LTPA levels through its down-regulating effects on hs-CRP and/or GlycA.

In the Brazilian Longitudinal Study of Adult Health (ELSA-Brasil), job stress (Santos et al., 2014) and LTPA (Oliveira et al., 2022; 2021) have been inversely associated with headache frequency and migraine occurrence. In the ELSA-Brasil's baseline sample, physical activity levels are inversely associated with hs-CRP levels (Queiroz et al., 2020), while GlycA was associated with depression (Brunoni et al., 2020). Thus, the ELSA-Brasil study offers unique opportunity to study the direct and indirect effects of job stress, LTPA, and hs-CRP/GlycA levels, as well as their interplay on headache disorders.

Therefore, we aimed at conducting a sequential mediation analysis model to test the influence of LTPA and its interaction with the systemic chronic inflammation biomarkers hs-CRP and GlycA on the job stress-headache disorders link in the ELSA-Brasil baseline cohort. We hypothesized that higher job stress, lower LTPA levels, and higher hs-CRP/GlycA levels would be associated with these conditions, whereas the job stress-headache disorders relationship would be indirectly mediated by LTPA levels and its downregulating effects on hs-CRP/GlycA levels.

2. Methods

2.1. Study design and population

This study is a cross-sectional analysis of the baseline data (2008–2010) from the ELSA-Brasil study (Aquino et al., 2012). In Brief, ELSA-Brasil is a multicenter cohort study which recruited 15,105 active and retired civil servants aged between 35 and 74 years from six capitals within three macro-regions of Brazil (São Paulo, Rio de Janeiro, Belo Horizonte, Salvador, Porto Alegre, and Vitória). Baseline data were retrieved from workplace-based interviews and clinic visits for biochemical sampling and assessments conducted between August 2008 and December 2010.

Exclusion criteria were current or recent pregnancy (<4 months prior to 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). In this analysis, we only included employees currently working at baseline (n = 12,069). We excluded participants with other primary headaches (probable migraine and probable TTH) or secondary headaches, as well as participants whose plasma concentrations of hs-CRP were indicative of potential infection or injury, defined as ≥10 mg/L (Kushner et al., 2006).

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 STROBE guidelines for reporting data from observational research.

2.2. Study variables

2.2.1. Headache disorders

All participants who answered "yes" to the question "In the last 12 months, did you have a headache?" were invited to answer a detailed headache questionnaire validated and previously used in Brazil (Benseñor et al., 1997), based on the 2nd Edition of the International

Table 2
Estimates of the associations between DCSQ subscales scores, headache disorders, LTPA, and hs-CRP (n = 7,466).

		Model 1		Model 2		Model 3	
	Path	**B (95 % CI)**	**S.E.**	**B (95 % CI)**	**S.E.**	**B (95 % CI)**	**S.E**
Demand							
	a_1	1.3190 (−0.5187, 3.1566)	0.9374	1.6117 (−0.2248, 3.4483)	0.9369	1.1617 (−0.6576, 2.9810)	0.9281
	a_2	−0.0020 (−0.0221, 0.0181)	0.0103	−0.0040 (−0.9765, 0.1988)	0.0103	−0.0073 (−0.0260, 0.0114)	0.0095
	d	**−0.0009 (−0.0011, −0.0006)** †	**0.0001**	**−0.0008 (−0.0241, 0.0161)** †	**0.0001**	**−0.0005 (−0.0007, −0.0002)** †	**0.0001**
Migraine	c'	**0.0469 (0.0156, 0.0781)** #	**0.0160**	**0.0383 (0.0067, 0.0700)** *	**0.0161**	**0.0390 (0.0074, 0.0706)** *	**0.0161**
	b_1	**−0.0009 (−0.0014, −0.0005)** †	**0.0002**	**−0.0007 (−0.0012, −0.0003)** #	**0.0002**	**−0.0006 (−0.0011, −0.0001)** *	**0.0002**
	b_2	0.0054 (−0.0264, 0.0373)	0.0162	0.0043 (−0.0369, 0.0283)	0.0166	0.0054 (−0.0307, 0.0414)	0.0184
TTH	c'	−0.0070 (−0.0264, 0.0124)	0.0099	−0.0044 (0.0238, 0.0151)	0.0099	−0.0090 (−0.0287, 0.0107)	0.0100
	b_1	0.0000 (−0.0003, 0.0002)	0.0001	−0.0001 (−0.0003, 0.0002)	0.0001	−0.0002 (−0.0005, 0.0000)	0.0001
	b_2	−0.0184 (−0.0403, 0.0035)	0.0112	−0.0167 (−0.0387, 0.0052)	0.0112	−0.0091 (−0.0330 0.0147)	0.0122
Control							
	a_1	**6.3129 (4.8624, 7.7633)** †	**0.7399**	**5.9955 (4.5416, 7.4494)** †	**0.7417**	**1.9047 (0.2379, 3.5715)** *	**0.8503**
	a_2	**−0.0290 (−0.0450, −0.0130)** †	**0.0082**	**−0.0267 (−0.0427, −0.0107)** #	**0.0082**	0.0088 (−0.0084, 0.0259)	0.0087
	d	**−0.0008 (−0.0011, −0.0006)** †	**0.0001**	**−0.0008 (−0.0010, −0.0005)** †	**0.0001**	**−0.0005 (−0.0007, −0.0002)** †	**0.0001**
Migraine	c'	**−0.0545—0.0785, −0.0305)** †	**0.0123**	**−0.0418 (−0.0664, −0.0171)** †	**0.0126**	**−0.0296 (−0.0577, −0.0015)** *	**0.0144**
	b_1	**−0.0008 (−0.0013, −0.0003)** †	**0.0002**	**−0.0006 (−0.0011, −0.0002)** #	**0.0002**	**−0.0006 (−0.0010, −0.0001)** *	**0.0002**
	b_2	0.0029 (−0.0290, 0.0348)	0.0163	0.0062 (−0.0389, 0.0264)	0.0167	0.0055 (−0.0306, 0.0415)	0.0184
TTH	c'	**0.0401 (0.0245, 0.0556)** †	**0.0079**	**0.0374 (0.0218, 0.0530)** †	**0.0080**	−0.0017 (−0.0197, 0.0163)	0.0092
	b_1	−0.0001 (−0.0003, 0.0002)	0.0001	−0.0001 (−0.0003, 0.0001)	0.0001	−0.0002 (−0.0005, 0.0000)	0.0001
	b_2	−0.0161 (−0.0381, 0.0058)	0.0112	−0.0147 (−0.0367, 0.0072)	0.0112	−0.0090 (−0.0329, 0.0149)	0.0122
Support							
	a_1	−0.6047 (−1.9612, 0.7519)	0.6920	−1.0637 (−2.4265, 0.2992)	0.6952	−0.1290 (−1.4936, 1.2357)	0.6961
	a_2	0.0090 (−0.0058, 0.0239)	0.0076	0.0124 (−0.0025, 0.0273)	0.0076	0.0089 (−0.0051, 0.0229)	0.0072
	d	**−0.0009 (−0.0011, −0.0006)** †	**0.0001**	**−0.0008 (−0.0011, −0.0006)** †	**0.0001**	**−0.0005 (−0.0007, −0.0002)** †	**0.0001**
Migraine	c'	**−0.0530 (−0.0746, −0.0314)** †	**0.0110**	**−0.0369 (−0.0589, −0.0149)** #	**0.0112**	**−0.0405 (−0.0628, −0.0183)** †	**0.0113**
	b_1	**−0.0009 (−0.0014, −0.0005)** †	**0.0002**	**−0.0007 (−0.0012, −0.0003)** #	**0.0002**	**−0.0006 (−0.0011, −0.0001)** *	**0.0002**
	b_2	0.0053 (−0.0266, 0.0372)	0.0163	−0.0043 (−0.0370, 0.0283)	0.0167	0.0052 (−0.0309, 0.0413)	0.0184
TTH	c'	0.0024 (−0.0119, 0.0167)	0.0073	−0.0017 (−0.0162, 0.0127)	0.0074	0.0062 (−0.0085, 0.0209)	0.0075
	b_1	0.0000 (−0.0003, 0.0002)	0.0001	−0.0001 (−0.0003, 0.0002)	0.0001	−0.0002 (−0.0005, 0.0000)	0.0001
	b_2	−0.0184 (−0.0403, 0.0035)	0.0112	−0.0166 (−0.0386, 0.0053)	0.0112	−0.0092 (−0.0330, 0.0147)	0.0122

*: p-value < 0.05;#: p-value < 0.01; †: p-value < 0.001; TTH: Tension-type headache; LTPA: Leisure-time physical activity; DCSQ: Demand, Control, and Support Questionnaire; Model 1: Age- and sex-adjusted; Model 2: Adjusted for age, sex, depression, and anxiety; Model 3: Adjusted for age, sex, depression, and anxiety, income, education, race, marital status, smoking status, and BMI; Path a_1 = DCSQ score → LTPA; Path a_2 = DCSQ score → hs-CRP; Path d = LTPA → hs-CRP; Path ć = DCSQ score → Headache Disorders; Path b_1 = LTPA → Headache Disorders; Path b_2 = hs-CRP → Headache Disorder.

Classification of Headache Disorders – ICHD-II, (Headache Classification Subcommittee of the International Headache Society, 2004). Briefly, it investigates pain frequency, duration, quality, location, intensity, triggering factors, and accompanying symptoms, such as nausea and/or vomiting. Participants fulfilling all ICHD-II criteria for migraine and TTH were classified accordingly.

2.2.2. Job stress

Job stress was evaluated using the 17-item Swedish Demand-Control-Support Questionnaire (DCSQ). The questionnaire consists of subscales measuring psychological job demand, job control, and social support domains. Responses were provided on a 4-point Likert scale (Johnson and Hall, 1988; Karasek, 1979). The job DCSQ demand subscale includes four questions measuring time and speed for performing tasks and one assessing conflicts between different demands. The job DCSQ control subscale includes four questions related to the use and development of abilities and two related to decision latitude in relation to the work process. The social DCSQ support subscale includes six questions regarding work colleagues' and supervisors' feedback and support (Suppl. Table S1). The DCSQ scores range from 5 to 20 in the demand subscale, and from 6 to 24 in the control and support subscales (Johnson and Hall, 1988; Karasek, 1979). The Brazilian version of DCSQ has been validated and demonstrated good reliability, with intraclass correlation coefficients of 0.88, 0.87 and 0.86 and Cronbach's alpha coefficients of 0.72, 0.63 and 0.86 for the demand, control and social support domains, respectively (Alves et al., 2004). This study's DCSQ scores were inverted from original score values, except for item C4 in the control subscale (Suppl. Table S1). As a result, "higher stress" in each subscale would be indicated by elevated scores in the demand subscale and reduced scores in the control and support subscales.

Based on Karaseḱs model, job demand and job control domains within the ELSA-Brasil study were divided into two categories: low (up to the median value) or high (above the median value) (Karasek, 1979). Participants were then sorted into four quadrants that characterize the combinations between job demand and control as follows: (1) low-strain work (low demand/high control), (2) passive (low demand/low control), (3) active (high demand/high control), and (4) high-strain work (high demand/low control) (Karasek, 1979; Santos et al., 2014) (Suppl. Figure S1).

Table 3
Bootstrap results of the sequential indirect effects of LTPA and hs-CRP on the associations between headache disorders and DCSQ subscales (n = 7,466).

	Paths	Model 1				Model 2				Model 3			
		Effect	S.E.	LL CI	UL CI	Effect	S.E.	LL CI	UL CI	Effect	S.E.	LL CI	UL CI
DCSQ Demand													
Migraine	a_1b_1	−0.0012	0.0010	−0.0034	0.0005	−0.0012	0.0008	−0.0031	0.0001	−0.0007	0.0007	−0.0024	0.0004
	a_2b_2	0.0000	0.0002	−0.0004	0.0004	0.0000	0.0002	−0.0004	0.0005	0.0000	0.0002	−0.0006	0.0004
	a_1db_2	0.0000	0.0000	−0.0001	0.0000	0.0000	0.0000	0.0000	0.0001	0.0000	0.0000	0.0000	0.0000
TTH	a_1b_1	0.0000	0.0002	−0.0005	0.0004	−0.0001	0.0002	−0.0007	0.0004	−0.0003	0.0003	−0.0010	0.0001
	a_2b_2	0.0000	0.0002	−0.0005	0.0005	0.0001	0.0002	−0.0004	0.0006	0.0001	0.0002	−0.0002	0.0005
	a_1db_2	0.0000	0.0000	0.0000	0.0001	0.0000	0.0000	0.0000	0.0001	0.0000	0.0000	0.0000	0.0000
DCSQ Control													
Migraine	a_1b_1	**−0.0051**	**0.0018**	**−0.0088**	**−0.0020**	**−0.0039**	**0.0016**	**−0.0074**	**−0.0010**	−0.0011	0.0007	−0.0028	0.0000
	a_2b_2	−0.0001	0.0005	−0.0010	0.0009	0.0002	0.0005	−0.0007	0.0011	0.0000	0.0002	−0.0004	0.0005
	a_1db_2	0.0000	0.0001	−0.0002	0.0002	0.0000	0.0001	−0.0001	0.0002	0.0000	0.0000	0.0000	0.0000
TTH	a_1b_1	−0.0005	0.0008	−0.0021	0.0011	−0.0006	0.0008	−0.0022	0.0008	−0.0004	0.0003	−0.0012	0.0001
	a_2b_2	0.0005	0.0004	−0.0001	0.0013	0.0004	0.0003	−0.0002	0.0012	−0.0001	0.0002	−0.0005	0.0002
	a_1db_2	0.0001	0.0001	0.0000	0.0002	0.0001	0.0001	0.0000	0.0002	0.0000	0.0000	0.0000	0.0000
DCSQ Support													
Migraine	a_1b_1	0.0006	0.0007	−0.0008	0.0020	0.0008	0.0006	−0.0003	0.0022	0.0001	0.0005	−0.0010	0.0011
	a_2b_2	0.0000	0.0002	−0.0003	0.0005	−0.0001	0.0002	−0.0006	0.0004	0.0000	0.0002	−0.0004	0.0005
	a_1db_2	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000
TTH	a_1b_1	0.0000	0.0001	−0.0003	0.0003	0.0001	0.0002	−0.0003	0.0004	0.0000	0.0002	−0.0004	0.0004
	a_2b_2	−0.0002	0.0002	−0.0007	0.0001	−0.0002	0.0002	−0.0007	0.0001	−0.0001	0.0002	−0.0004	0.0002
	a_1db_2	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	−0.0001	0.0000	0.0000	0.0000	0.0000	0.0000

TTH: Tension-type headache; LTPA: Leisure-time physical activity; DCSQ: Demand Control Support Questionnaire; CI: Confidence interval; LL: lower limit; UL: Upper limit; Bold numbers indicate sequential indirect mediating effects, wherein the CI around the indirect effects obtained through bootstrapping exclude zero, that is, remain above (positive values) or below (negative values) zero. Model 1: Age- and sex-adjusted; Model 2: Adjusted for age, sex, depression, and anxiety; Model 3: Adjusted for age, sex, depression, and anxiety, income, education, race, marital status, smoking status, and BMI; Path a_1b_1= DCSQ score → LTPA → Headache Disorder; Path a_2b_2 = DCSQ score → hs-CRP → Headache Disorder; Path a_1db_2 = DCSQ score → LTPA → hs-CRP → Headache Disorder.

2.2.3. Leisure-Time physical activity

LPTA was obtained by the International Physical Activity Questionnaire (IPAQ) long-form to gather information on levels of LTPA. In Brazil, the IPAQ had previously undergone translation and validation (Craig et al., 2003). The IPAQ has demonstrated satisfactory criterion validity, comparable to other self-report questionnaires ($r_{Spearman}$ = 0.30), and excellent reliability ($r_{Spearman}$ = 0.80) (Craig et al., 2003). The IPAQ long-form version used here has shown acceptable criterion validity (pooled $\rho_{Spearman}$ = 0.30) against an accelerometer (CSA model 7164) across 12 countries, including Brazil (Craig et al., 2003). When compared to accelerometer-measured physical activity (PA), the IPAQ exhibited strong validity for overall physical activity levels ($r_{Spearman}$ = 0.55) and vigorous physical activity ($r_{Spearman}$ = 0.71), while displaying a weaker relationship for moderate physical activity ($r_{Spearman}$ = 0.21) (Hagströmer et al., 2006).

Within the LTPA domain, the questionnaire inquiries about the frequency of physical activities during leisure time (e.g., "During the last 7 days, on how many days did you engage in moderate physical activities during your leisure time?"). The LTPA levels were calculated by multiplying the weekly frequency (number of days) by the duration (minutes per day) of the reported physical activity, expressed as minutes per week ($min.week^{-1}$).

2.2.4. Biomarkers: hs-CRP and GlycA

Blood samples were collected from participants in the six research centers following an average overnight fasting period of 12 h (Bensenor et al., 2013). The samples were stored in dry tubes. To ensure consistent and reliable results, the samples were processed and analyzed in a central laboratory of the ELSA-Brasil study. The hs-CRP levels were measured using the quantitative nephelometry method (BN II, Siemens), and the results were reported in milligrams per liter (mg/L). The hs-CRP measurements were assessed both as continuous values and dichotomized into two categories (yes/no) if values met the definition of low-grade chronic inflammation of ≥3 mg/l (Kushner et al., 2006).

GlycA levels were quantified using nuclear magnetic resonance (NMR) spectra acquired from ethylenediaminetetraacetic acid (EDTA) plasma samples (Tebar et al., 2023). The samples were processed by LabCorp (Raleigh, NC, USA, former LipoScience), using a specialized platform known as the nuclear magnetic resonance Profiler and the amplitude of GlycA signal was converted to micromoles per liter (mmol/L) (Tebar et al., 2023). This platform includes a 9.4-T (400-MHz 1H frequency) spectrometer with an integrated fluidic sample delivery system. The measurement process involves the use of proprietary deconvolution software, which is designed to quantify the GlycA signal accurately. The intra-assay and inter-assay coefficients of variation for GlycA quantification are reported as 1.9 % and 2.6 %, respectively (Tebar et al., 2023). Additionally, the biological variability is low, with a coefficient of variation of 4.3 %. Information about the logistics and routine procedures of blood sampling in the ELSA-Brasil study are found elsewhere (Bensenor et al., 2013; Fedeli et al., 2013).

2.2.5. Sociodemographic and clinical variables

The study considered several covariate variables, including sociodemographic factors, lifestyle factors, mental health and medical comorbidities, and use of migraine prophylactic medication. Sociodemographic variables encompassed sex assigned at birth (Female or Male), age (years), body mass index (BMI) household income (<US $1,245, US$1,245–3,319, and >US$3,319), educational level (elementary, high school, or college), race determined by self-identified skin color (White, Black, Brown or Pardo, Others – Indigenous, Asian), and marital status (married, separated, single, widow/widower, or other). The race in the Brazilian population is based on participants' self-identification, a methodology adopted in Brazilian Census and epidemiological studies, as it takes account of historical and theoretical context (Instituto Brasileiro de Geografia e Estatística - IBGE, 2010; Oliveira et al., 2023).

Smoking status was evaluated as lifestyle variable (never, former, current). Depression and generalized anxiety disorder were evaluated using the Brazilian-Portuguese version of the Clinical Interview Schedule – Revised (CIS-R) (Nunes et al., 2011), and diagnoses were

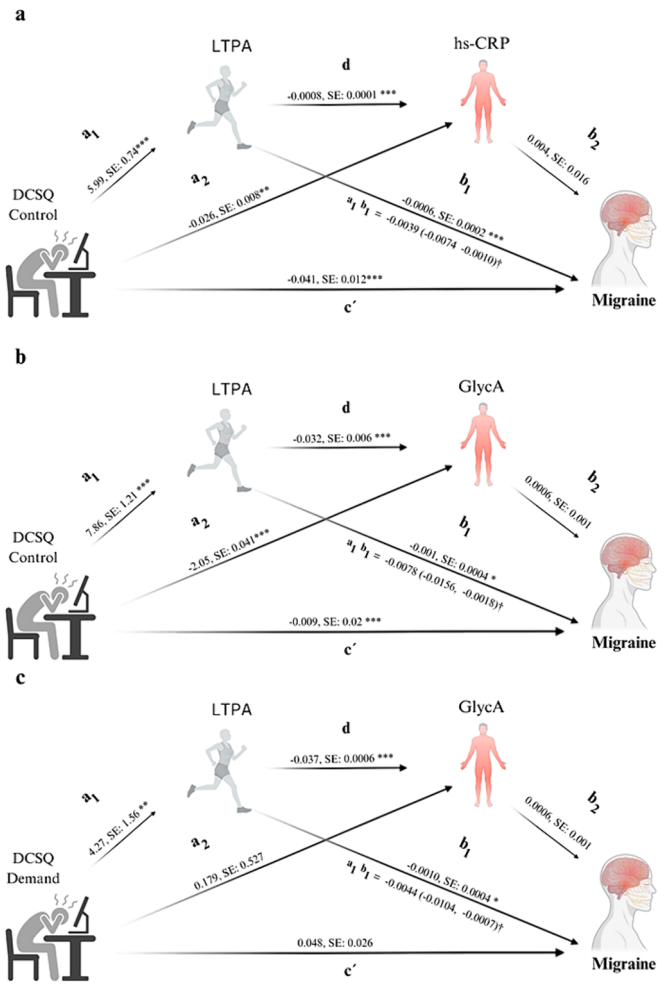

Fig. 2. (a-c). Indirect mediating effects of LTPA and systemic inflammation biomarkers in the job stress-migraine relationship. TTH: Tension-type headache; LTPA: Leisure-time physical activity; hs-CRP: High-sensitivity C-reactive Protein; GlycA: Acute phase glycoproteins; DCSQ: Demand Control Support Questionnaire; *: p-value < 0.05; **: p-value < 0.01; ***: p-value < 0.001, *vs* other groups pooled together; †: indicates sequential indirect mediating effects, wherein the confidence intervals around the indirect effects obtained through bootstrapping exclude zero. Path a_1b_1= DCSQ score → LTPA → Headache Disorder, adjusted for age, sex, depression, and anxiety (Model 2).

established by applying specific cut-off values and criteria outlined in the International Classification of Diseases (ICD-10). BMI was determined by dividing weight (in kilograms) by the square value of height (in meters).

Cardiovascular and cerebrovascular diseases included self-reported previous medical history about many clinical conditions such as myocardial infarct, heart failure, angina pectoris, Chagaśs disease, thrombosis, or embolism and cerebrovascular (stroke). We gathered information on cardiometabolic comorbidities, by assessing blood pressure, fasting glycemia, total cholesterol and its components, triglycerides, glycosylated hemoglobin, insulin, and the HOMA-IR index, based on established anthropometric and laboratory techniques (Bensenor et al., 2013). Participants having a prior medical history of high blood pressure who satisfied the requirements of a systolic blood pressure of at least 140 mmHg and/or a diastolic blood pressure of at least 90 mmHg, or who were taking medication for hypertension, were evaluated for a diagnosis of hypertension. The diagnosis of diabetes was made using a combination of the patient's medical history, the medications they were taking, and the cutoff points for hemoglobin A1C (HbA1C) levels ≥6.5 %, two-hour plasma glucose ≥200 mg/dl, and fasting plasma glucose ≥126 mg/dl. The National Cholesterol Program-Adult Treatment Panel III (NCEP ATP III) set criteria for the definitions of dyslipidemia, metabolic syndrome, and obesity (Grundy et al., 2004).

2.3. Statistical analysis

Descriptive statistics of sociodemographic, lifestyle, comorbidities, clinical, hs-CRP levels, and DCSQ subscales scores are reported as a percentage (%), or mean (95 % CI), according to variable features. One-way ANOVA (continuous variables), with Bonferroni corrections was adopted for pairwise comparisons. The inspection of histograms, Q-Q plots, and P-P plots were conducted to examine continuous variables and ensure their adherence to the assumption of a normal distribution. The variables presenting non-normal distribution were log-transformed and are reported accordingly. For categorical variables, comparisons between groups were performed by Chi-squared test or Kruskal Wallis test, the later in the case of variables that violated the assumption of normal distribution.

To inspect the correlations between the variables of interest, estimates of Pearson's bivariate correlations between LTPA, hs-CRP, and DCSQ subscales were computed.

Conditional process analyses were used with a sequential mediation approach to explore the associations between variables of interest. In these analyses, ordinary least squares regressions were performed to estimate the path coefficients for each regression composing the models' framework.

In our models, the DCSQ scores were set as independent variable (X) and the diagnoses of headache disorders were set as the outcome variable (Y). Migraine, TTH, and no headache groups were transformed into two binary variables (dummy variables). As such, each headache disorder was chosen separately as a comparison category against the remaining groups. The mediator variables were LTPA (M_1) and hs-CRP or GlycA (M_2). We computed the sequential indirect effects of each mediator and their interplay on headache diagnosis. The continuous variables LTPA, hs-CRP or GlycA, and DCSQ scores were mean-centered to avoid multicollinearity issues. We performed a series of regression models – one for each headache disorder set as outcome and for each DCSQ subscale set as "predictor", to obtain the estimates of paths coefficients a_1 (X → M_1), d (M_1 → M_2), b_1 (M_1 → Y), a_2 (X → M_2), b_2 (M_2 → Y). Path coefficients (a_1, b_1, a_2, b_2, and d) with standard error (SE) were calculated. The Suppl. Figure S2 illustrates the schematic representation of the sequential mediation analysis adopted in this study. The confidence intervals (CI) around the sequential indirect effects (paths a_1b_1, a_2b_2, and a_1db_2) were computed and were obtained using bootstrapping procedure for 5,000 random samples. In the context of mediation analysis, bootstrapping is used to estimate the CIs for indirect effects. In this context, the definition of "effect" refers to the quantifiable change in the association coefficient of X → Y after the inclusion of M, or in the case of sequential analysis, M_1 and M_2 (Hayes, 2022). Since the outcome variable was binary across the models, log-odds were computed for the direct and indirect effects of X and M variables on Y. Full indirect effects were assumed if there were indirect effects of mediator variables but no significant association of DCSQ subscales on headache disorders (ć path). Partial indirect effects were assumed if there were significant indirect effects of mediator variables and significant association of DCSQ subscales on headache disorders.

To examine the impact of confounding variables, we conducted a set of three distinct models for each DCSQ subscale and for each inflammatory biomarker set as mediator M_2. The first model (Model 1) was adjusted for age and sex. In the second (Model 2), further adjusted for mental health comorbidities, specifically depression and generalized anxiety disorder (GAD), and the third models (Model 3) further adjusted for income, education, race, marital status, smoking status, and body mass index (BMI).

To further control for the effects of major chronic diseases, sensitivity analyses were performed by running the same regression models

Table 4
Estimates of the associations between DCSQ subscales scores, headache disorders, LTPA, and GlycA (n = 2.376).

		Model 1		Model 2		Model 3	
	Path	**B (95 % CI)**	**S.E.**	**B (95 % CI)**	**S.E.**	**B (95 % CI)**	**S.E**
Demand							
	a_1	**4.1542 (1.0678, 7.2406)** #	**1.5739**	**4.2726 (1.1944, 7.3507)** #	**1.5697**	**3.7977 (0.7372, 6.8582)** *	**1.5607**
	a_2	0.2394 (−0.7985, 1.2773)	0.5293	0.1798 (−0.8545, 1.2142)	0.5275	0.3285 (−0.6567, 1.3138)	0.5024
	d	**−0.0400 (−0.0535, −0.0265)** †	**0.0069**	**−0.0375 (−0.0510, −0.0240)** †	**0.0069**	**−0.0248 (−0.0377, −0.0118)** †	**0.0066**
Migraine	c'	0.0507 (−0.0009, 0.1024)	0.0264	0.0487 (−0.0037, 0.1012)	0.0268	0.0499 (−0.0027, 0.1025)	0.0268
	b_1	**−0.0012 (−0.0021, −0.0004)** #	**0.0004**	**−0.0010 (−0.0019, −0.0002)** *	**0.0004**	**−0.0009 (−0.0018, −0.0001)** *	**0.0004**
	b_2	0.0012 (−0.0007, 0.0031)	0.0010	0.0006 (−0.0014, 0.0025)	0.0010	0.0007 (−0.0014, 0.0027)	0.0011
TTH	c'	−0.0251 (−0.0589, 0.0086)	0.0172	−0.0242 (−0.0580, 0.0095)	0.0172	−0.0299 (−0.0641, 0.0043)	0.0174
	b_1	−0.0001 (−0.0005, 0.0003)	0.0002	−0.0001 (−0.0006, 0.0003)	0.0002	−0.0002 (−0.0007, 0.0002)	0.0002
	b_2	**−0.0022 (−0.0036, −0.0009)** †	**0.0007**	**−0.0021 (−0.0034, −0.0008)** #	**0.0007**	**−0.0016 (−0.0031, −0.0002)**	**0.0007**
Control							
	a_1	**7.4754 (5.0824, 9.8684)** †	**1.2203**	**7.8680 (5.4767, 10.2594)** †	**1.2195**	**5.0347 (2.3110, 7.7583)** †	**1.3889**
	a_2	**−2.4692 (−3.2768, −1.6617)** †	**0.4118**	**−2.0547 (−2.8656, −1.2438)** †	**0.4135**	−0.3539 (−1.2334, 0.5255)	0.4485
	d	**−0.3041 (−0.4225, −0.1857)** †	**0.0604**	**−0.0329 (−0.0464, −0.0193)** †	**0.0069**	**−0.0242 (−0.0372, −0.0112)** †	**0.0066**
Migraine	c'	−0.0213 (−0.0611, 0.0186)	0.0203	−0.0092 (−0.0501, 0.0318)	0.0209	0.0140 (−0.0317, 0.0597)	0.0233
	b_1	**−0.0011 (−0.0020, −0.0003)** #	**0.0004**	**−0.0010 (−0.0018, −0.0002)** *	**0.0004**	**−0.0009 (−0.0018, −0.0001)** *	**0.0004**
	b_2	0.0011 (−0.0008, 0.0030)	0.0010	0.0006 (−0.0014, 0.0025)	0.0010	0.0007 (−0.0014, 0.0028)	0.0011
TTH	c'	0.0241 (−0.0027, 0.0508)	0.0136	0.0219 (−0.0049, 0.0487)	0.0137	0.0103 (−0.0407, 0.0202)	0.0155
	b_1	−0.0002 (−0.0006, 0.0003)	0.0002	−0.0002 (−0.0006, 0.0003)	0.0002	−0.0003 (−0.007, 0.0002)	0.0002
	b_2	**−0.0021 (−0.0035, −0.0008)** #	**0.0007**	**−0.0020 (−0.0033, −0.0007)** #	**0.0007**	**−0.0017 (−0.0031, −0.0003)** *	**0.0007**
Support							
	a_1	−1.2666 (−3.5179, 0.9847)	1.1481	−1.7781 (−4.0369, 0.4807)	1.1519	−0.7084 (−2.9752, 1.5583)	1.1519
	a_2	−0.4127 (−1.1679, 0.3424)	0.3851	−0.2183 (−0.9757, 0.5391)	0.3862	−0.4495 (−1.1773, 0.2784)	0.3712
	d	**−0.0400 (−0.0535, −0.0265)** †	**0.0069**	**−0.0375 (−0.0510, −0.0240)** †	**0.0069**	**−0.0247 (−0.0376, −0.0117)** #	**0.0069**
Migraine	c'	**−0.0594 (−0.0942, −0.0246)** †	**0.0178**	**−0.0471 (−0.0825, −0.0118)** #	**0.0180**	**−0.0519 (−0.0875, −0.0163)** #	**0.0182**
	b_1	**−0.0012 (−0.0021, −0.0004)** #	**0.0004**	**−0.0011 (−0.0019, −0.0002)** *	**0.0004**	**−0.0009 (−0.0018, −0.0001)** *	**0.0004**
	b_2	0.0012 (−0.0008, 0.0031)	0.0010	0.0006 (−0.0014, 0.0025)	0.0010	0.0006 (−0.0015, 0.0027)	0.0011
TTH	c'	0.0156 (−0.0089, 0.0402)	0.0125	0.0123 (−0.0124, 0.0371)	0.0126	0.0205 (−0.0047, 0.0458)	0.0129
	b_1	−0.0001 (−0.0005, 0.0003)	0.0002	−0.0001 (−0.0006, 0.0003)	0.0002	−0.0003 (−0.0007, 0.0002)	0.0002
	b_2	**−0.0022 (−0.0036, −0.0009)** †	**0.0007**	**−0.0021 (−0.0034, −0.0008)** #	**0.0007**	**−0.0016 (−0.0030, −0.0002)** *	**0.0007**

*: p-value < 0.05; #: p-value < 0.01; †: p-value < 0.001; TTH: Tension-type headache; LTPA: Leisure-time physical activity; DCSQ: Demand, Control, and Support Questionnaire; Model 1: Age- and sex-adjusted; Model 2: Adjusted for age, sex, depression, and anxiety; Model 3: Adjusted for age, sex, depression, and anxiety, income, education, race, marital status, smoking status, and BMI; Path a_1 = DCSQ score → LTPA; Path a_2 = DCSQ score → GlycA; Path d = LTPA → GlycA; Path ć = DCSQ score → Headache Disorders; Path b_1 = LTPA → Headache Disorders; Path b_2 = GlycA → Headache Disorder.

excluding participants with cardiometabolic diseases (i.e., cardiovascular disease, stroke, hypertension, diabetes, dyslipidemia, or metabolic syndrome).

Descriptive statistics and Pearsońs bivariate correlations were run in the SPSS software (IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY). The PROCESS macro (v4.0) for SPSS created by Hayes (Hayes, 2022) was used for the conditional process analyses. For all tests, a two-tailed p value < 0.05 was considered statistically significant.

3. Results

Of 15,105 participants in the ELSA-Brasil baseline cohort, 12,096 participants were current workers in the ELSA-Brasil baseline assessment. Of these, 7,466 provided full data on the socioeconomic, clinical, lifestyle and DCSQ variables, and were analyzed in this study. Participants' flow in the study is illustrated in Fig. 1.

Table 1 shows the main baseline characteristics by headache status of ELSA-Brasil participants. Overall, mean age was 49.3 (95 % CI: 49.3–49.6) years and 45.6 % of our sample was constituted by female. The frequencies of migraine and TTH were 13.1 % and 49.4 % of sample. Overall, headache disorders groups showed a higher proportion of participants female, younger, of middle-income strata, with lower physically active level, and with higher frequency of mental health disorders, compared to their counterparts without headache disorders. The migraine group showed higher frequency of mental health disorders and lower LTPA levels than participants with TTH (Table 1). Still, the migraine group showed higher hs-CPR, GlycA, and DCSQ scores in the Demand subscale, and lower scores in the DSCQ Control and support subscales, indicating higher job stress levels in all domains compared to those with no headache and TTH (Table 1). The TTH group showed lower scores in the DSCQ Support subscale than no control group. There was a higher proportion of participants with migraine with high-strain jobs, and lower proportion of participants with migraine and TTH in passive jobs (Table 1).

In the total sample, LTPA was inversely correlated with hs-CRP (r = −0.089, p < 0.001) and GlycA (r = −0.125, p < 0.001) levels and positively correlated with DCSQ Control scores (r = 0.083, p < 0.001) (Suppl. Table S2). DCSQ Control scores was inversely correlated with hs-CRP (r = −0.034, p < 0.001) and GlycA (r = −0.123, p < 0.001) levels (Suppl. Table S2).

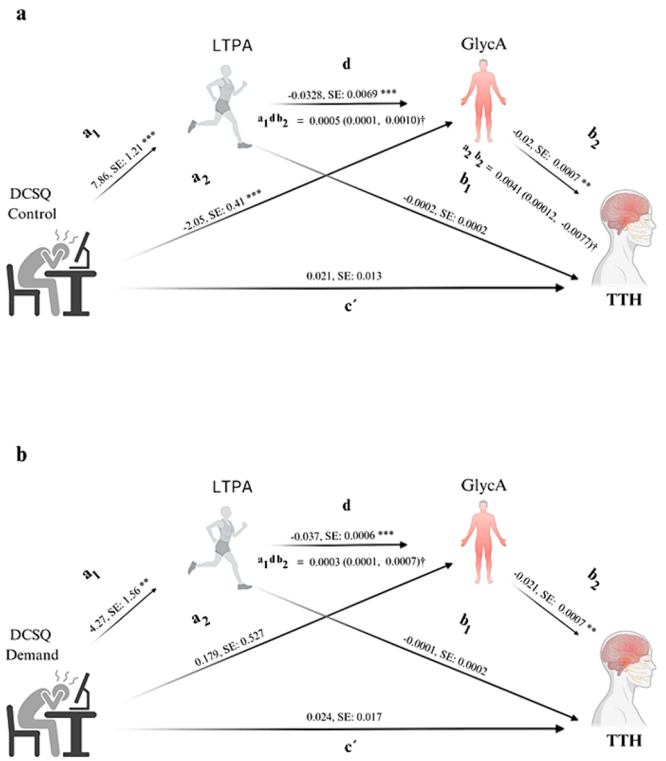

Fig. 3. (a-b). Indirect mediating effects of LTPA and GlycA in the job stress-TTH relationship. TTH: Tension-type headache; LTPA: Leisure-time physical activity; GlycA: Acute phase glycoproteins; DCSQ: Demand Control Support Questionnaire; *: p-value <0.05; **: p-value <0.01; ***: p-value <0.001, *vs* other groups pooled together; †: indicates sequential indirect mediating effects, wherein the confidence intervals around the indirect effects obtained through bootstrapping exclude zero. Path a2b2 = DCSQ score → GlycA → Headache Disorder; Path a1db2 = DCSQ score → LTPA → GlycA → Headache Disorder, adjusted for age, sex, depression, and anxiety (Model 2).

3.1. Associations between DCSQ scores, Headache, LTPA, and hs-CRP

The Model 1 (age- and sex-adjusted) and Model 2 (adjusted for age, sex, anxiety, and depression) showed a similar pattern of associations between DCSQ subscales and headache disorders (Table 2). In the Model 2, a higher psychosocial job stress in all subscales was associated with migraine, while DCSQ Control was positively associated with TTH [c' = 0.037 (0.021, 0.053), p < 0.001] (Table 2). That is, higher demand and lower control and support increased the susceptibility to migraine, whereas higher control was associated with higher susceptibility of TTH.

The DCSQ Control scores were positively associated with LTPA levels [a_1 = 5.99 (4.54, 7.44), p < 0.001) and inversely associated with hs-CRP levels (a_2 = −0.026 (−0.042, −0.010), p = 0.001), indicating that higher control increased the likelihood of higher LTPA and lower hs-CRP levels.

LTPA levels were inversely associated with migraine [b_1 = −0.0006 (−0.0011, −0.0002), p = 0.006] (Table 2), indicating that higher LTPA levels decreased the susceptibility to migraine.

In the fully adjusted models (Model 3) with sociodemographic (age, sex, income, education, race, marital status), smoking status, BMI, and mental health comorbidities concomitantly included in the equations, all DCSQ scores remained associated with migraine (Table 2). The LTPA levels remained inversely associated with migraine [b_1 = −0.0006, (−0.0011, −0.0001), p = 0.013] and hs-CRP levels [d = −0.0005, (−0.0007, −0.0002), p < 0.001], while DCSQ Control scores remained positively associated with LTPA levels [a_1 = 1.90 (0.23, 3.57), p = 0.025] (Table 2).

3.1.1. Mediating effects of LTPA and hs-CRP on the job Stress-Headache link

Based on the bootstrapping procedure results of paths effects, the Model 2 showed that there was a partial, indirect mediating effect of LTPA but not hs-CRP levels on the associations of DCSQ Control scores with migraine [a_1b_1: −0.0039 (−0.0074, −0.0010)] (Table 3), indicating that higher LTPA levels reversed the negative association between job stress in this domain and migraine, regardless of hs-CRP levels (Fig. 2a).

The indirect mediating effect of LTPA on the job stress (job control)-migraine relationship remained significant in the sensitivity analysis after excluding participants with cardiometabolic diseases [a_1b_1: −0.0034 (−0.0077, −0.0002)] in the Model 2. No indirect mediating effect remained significant in Model 3 after full adjustments (Table 3).

3.2. Associations between DCSQ scores, Headache, LTPA, and GlycA

In the subsample with data on GlycA (n = 2,367), only DCSQ Support was significantly and inversely associated with migraine in all models, indicating that higher support decreased the susceptibility to migraine, while no DCSQ subscale was associated with TTH in any model (Table 5).

In the Model 2, the DCSQ Control scores was positively associated with LTPA levels [a_1 = 7.475 (5.082, 9.868), p < 0.001) and inversely associated with GlycA levels (a_2 = −0.029 (−0.045, −0.013), p < 0.001), indicating that higher control increased the likelihood of higher LTPA and lower GlycA levels.

LTPA levels were inversely associated with migraine [b_1 = −0.032 (−0.046, −0.0193), p < 0.001] (Table 4), indicating that higher LTPA levels decreased the susceptibility to migraine.

In the fully adjusted models (Model 3), the LTPA levels remained inversely associated with migraine [b_1 = −0.0009 (−0.0018, −0.0001), p = 0.03] and GlycA levels [d = −0.024 (−0.037, −0.011), p < 0.001], while DCSQ Control scores remained positively associated with LTPA levels [a_1 = 5.03 (2.31, 7.75), p < 0.001] (Table 4).

3.2.1. Mediating effects of LTPA and GlycA on the job Stress-Headache link

Based on the bootstrapping procedure results of paths effects, the Model 2 showed that there was a full, indirect mediating effect of LTPA levels on the DCSQ Control-migraine [a_1b_1: −0.0078 (−0.0156, −0.0018)] (Fig. 2b) and DCSQ Demand-migraine [a_1b_1: −0.0044 (−0.0104, −0.0007)] (Fig. 2c) relationships, indicating that higher LTPA levels reversed the association between higher demand/lower control and migraine, regardless of GlycA levels.

For TTH, there was a full, indirect mediating effect of GlycA [a_1b_1: 0.0041 (0.0012, 0.0077)] and the interaction between LTPA and GlycA [a_1db_2: 0.0005 (0.0001, 0.0010)] on the DCSQ Control-TTH relationship (Fig. 3a), indicating that higher job control was associated with lower GlycA, which in turn associated with lower TTH, and that the effect of higher LTPA in reducing GlycA levels also associated with lower TTH. There was a full, indirect mediating effect of the interaction between LTPA and GlycA [a_1db_2: 0.0003 (0.0001, 0.0007)] on the DCSQ Demand-TTH relationship (Fig. 3b), indicating that lower job demand associated with TTH is mediated by the effects of higher LTPA in reducing GlycA levels.

For the models 2, only the full, indirect mediating effect of LTPA levels on the DCSQ Control-migraine [a_1b_1: −0.0068 (−0.0157, −0.0005)] relationship remained significant in the sensitivity analysis after excluding participants with cardiometabolic diseases. No indirect mediating effect remained significant after full adjustments (Table 5).

4. Discussion

In this study, we aimed at identifying whether the associations between psychosocial job stress and headache disorders would be mediated by the interplay between LTPA and systemic inflammation

Table 5
Bootstrap results of the sequential indirect effects of LTPA and GlycA on the associations between headache disorders and DCSQ subscales (n = 2.376).

	Paths	Model 1				Model 2				Model 3			
		Effect	S.E.	LL CI	UL CI	Effect	S.E.	LL CI	UL CI	Effect	S.E.	LL CI	UL CI
DCSQ Demand													
Migraine	a_1b_1	**−0.0051**	**0.0028**	**−0.0117**	**−0.0010**	**−0.0044**	**0.0025**	**−0.0104**	**−0.0007**	**−0.0035**	**0.0023**	**−0.0090**	**−0.0003**
	a_2b_2	0.0003	0.0009	−0.0015	0.0024	0.0001	0.0007	−0.0012	0.0017	0.0002	0.0008	−0.0011	0.0021
	a_1db_2	−0.0002	0.0002	−0.0007	0.0001	−0.0001	0.0002	−0.0005	0.0002	−0.0001	0.0001	−0.0003	0.0002
TTH	a_1b_1	−0.0004	0.0010	−0.0027	0.0014	−0.0006	0.0011	−0.0031	0.0013	−0.0009	0.0011	−0.0034	0.0007
	a_2b_2	−0.0005	0.0013	−0.0033	0.0020	−0.0004	0.0012	−0.0030	0.0019	−0.0005	0.0010	−0.0028	0.0012
	a_1db_2	**0.0004**	**0.0002**	**0.0001**	**0.0008**	**0.0003**	**0.0002**	**0.0001**	**0.0007**	0.0002	0.0001	0.0000	0.0004
DCSQ Control													
Migraine	a_1b_1	**−0.0086**	**0.0035**	**−0.0166**	**−0.0026**	**−0.0078**	**0.0035**	**−0.0156**	**−0.0018**	**−0.0047**	**0.0024**	**−0.0103**	**−0.0008**
	a_2b_2	−0.0028	0.0026	−0.0081	0.0021	−0.0011	0.0021	−0.0054	0.0031	−0.0002	0.0007	−0.0020	0.0010
	a_1db_2	−0.0009	0.0004	−0.0018	0.0002	−0.0001	0.0003	−0.0007	0.0004	−0.0001	0.0002	−0.0004	0.0002
TTH	a_1b_1	−0.0013	0.0018	−0.0049	0.0025	−0.0015	0.0018	−0.0051	0.0020	−0.0013	0.0012	−0.0039	0.0009
	a_2b_2	**0.0047**	**0.0018**	**0.0016**	**0.0084**	**0.0041**	**0.0017**	**0.0012**	**0.0077**	0.0006	0.0009	−0.0009	0.0027
	a_1db_2	**0.0006**	**0.0003**	**0.0002**	**0.0012**	**0.0005**	**0.0002**	**0.0001**	**0.0010**	0.0002	0.0001	0.0000	0.0005
DCSQ Support													
Migraine	a_1b_1	0.0016	0.0018	−0.0016	0.0057	0.0019	0.0017	−0.0008	0.0059	0.0007	0.0014	−0.0020	0.0039
	a_2b_2	−0.0005	0.0007	−0.0023	0.0006	−0.0001	0.0005	−0.0013	0.0008	−0.0003	0.0007	−0.0019	0.0009
	a_1db_2	0.0001	0.0001	−0.0001	0.0003	0.0000	0.0001	−0.0001	0.0002	0.0000	0.0001	−0.0001	0.0001
TTH	a_1b_1	0.0001	0.0004	−0.0006	0.0012	0.0003	0.0005	−0.0006	0.0016	0.0002	0.0005	−0.0007	0.0015
	a_2b_2	0.0009	0.0009	−0.0008	0.0030	0.0005	0.0009	−0.0012	0.0023	0.0007	0.0007	−0.0005	0.0025
	a_1db_2	−0.0001	0.0001	−0.0004	0.0001	−0.0001	0.0001	−0.0004	0.0001	−0.0001	0.0000	−0.0002	0.0001

TTH: Tension-type headache; LTPA: Leisure-time physical activity; DCSQ: Demand Control Support Questionnaire; CI: Confidence interval; LL: lower limit; UL: Upper limit; Bold numbers indicate sequential indirect mediating effects, wherein the CI around the indirect effects obtained through bootstrapping exclude zero, that is, remain above (positive values) or below (negative values) zero. Model 1: Age- and sex-adjusted; Model 2: Adjusted for age, sex, depression, and anxiety; Model 3: Adjusted for age, sex, depression, and anxiety, income, education, race, marital status, smoking status, and BMI; Path a_1b_1 = DCSQ score → LTPA → Headache Disorder; Path a_2b_2 = DCSQ score → GlycA → Headache Disorder; Path a_1db_2 = DCSQ score → LTPA → GlycA → Headache Disorder.

biomarkers. We confirmed other studies showing an inversed association between physical activity and both hs-CRP (Del Rosso et al., 2023; Fedewa et al., 2017; Hammonds et al., 2016; Papagianni et al., 2023; Ploeger et al., 2009; Queiroz et al., 2020) and GlycA (Barber et al., 2018), as well as the associations between domain-specific psychosocial job stress and headache disorders migraine (Leineweber et al., 2020; Mäki et al., 2008; Santos et al., 2014; Urhammer et al., 2020; Wei et al., 2023). The novelty of this study was the findings that LTPA but not hs-CRP or GlycA levels mediated the association of job control scores with migraine, while there was a sequential indirect effect of the interplay between LTPA and GlycA in the association between job control/demand and TTH, regardless of age, sex, and mental health comorbidities.

4.1. Migraine

Our findings contrast with the evidence in the HUNT study, which found a higher risk of migraine with higher hs-CRP levels (Hagen et al., 2020). Possibly, the higher cut-off values for hs-CRP levels set as exclusion criteria (≥20 mg/L in the HUNT study and ≥10 mg/L in the ELSA-Brasil study) and the difference in populations characteristics (working population in the ELSA-Brasil *vs* adults in general in the HUNT study) could explain these discrepant findings. Furthermore, our study does not suggest the involvement of GlycA with migraine and that LTPA may reduce the impact of psychosocial job stress on migraine occurrence independently of mechanisms involving hs-CRP and GlycA.

Agreeably, Oliveira et al., (2017a) found higher circulating levels of the pro-inflammatory cytokines tumor necrosis factor-alpha (TNF-α) and interleukin-12p70 (IL-12p70) associated with migraine, lower cardiorespiratory fitness, and higher anxiety scores in a small sample of women. Still, these authors later found a significant correlation between reductions in IL-12p70 levels, anxiety scores, and monthly migraine days after a 12-week aerobic exercise training program, suggesting that IL-12p70 might be implicated in the link between abnormal physiological and behavioral/psychological functioning of migraine (Oliveira et al., 2017b). Interestingly, the intraperitoneal administration of calcitonin gene-related peptide (CGRP) – a pro-inflammatory, vasoactive neuropeptide implicated in migraine pathophysiology and the main target of current prophylactic pharmacological treatment (Ashina et al., 2021), elicited reduced voluntary wheel activity and anxiety-like behavior in pre-clinical models of migraine (Sink et al., 2013; Wattiez et al., 2021), suggesting that CGRP also mediate the behavioral features of migraine. These findings merit further studies to identify specific mediators of the environmental and behavioral features of migraine in humans.

Alternatively, owing to the cross-sectional feature of this study, the mediating effect of LTPA in the link between lower job control and migraine may be explained in a few different ways. It may imply that workers with little control over their jobs may face challenges in participating in physical activities due to the encroachment of lack of job control into daily life (Griep et al., 2016; 2015), or that occupations characterized by low control, repetitious activities may trigger migraine and, hence, hamper physical activity behavior (Farris et al., 2019; 2018), or that low physical activity may predispose to higher psychosocial job stress (Emeny et al., 2012; Larsson et al., 2019) and migraine (Hagen et al., 2018; Master et al., 2022).

4.2. TTH

Regarding TTH, unlike migraine, its relationship with job control/demand was mediated by the interplay between LTPA and GlycA, suggesting that higher job control/lower job demand is associated with higher LTPA levels, which in turn reduced GlycA levels, and that this process is translated into lower TTH occurrence. Alternatively, this finding may implicate the assumption of reverse causality, that is, participants with TTH had predominantly jobs with higher control/lower demand, which allowed them to engage in LTPA more often, hence, inducing GlycA reductions. Either way, these finding suggest a potential involvement of GlycA in the link between job stress and TTH.

Importantly, higher job control is generally interpreted as reduced stress because it allows employees more autonomy and decision-making

power (Karasek, 1979). However, individuals with higher degree of control may also bear a significant amount of responsibility, which could paradoxically be translated into to higher stress due to excessive responsibility, perfectionism, conflict in decision-making, etc, which can hamper to engage in a healthy lifestyle. (Griep et al., 2016; 2015). In this context, our findings suggest that TTH occurrence due to job stress caused by high job control could be prevented by LTPA-induced downregulation of GlycA.

4.3. Clinical and public health implications

This study has clinical and epidemiological implications. Considering the therapeutic and anxiolytic effects of prescribed exercise on headache disorders (Krøll et al., 2018; Madsen et al., 2018; Oliveira et al., 2019; 2017b; Reina- et al., 2024; Reina-Varona et al., 2023; Woldeamanuel and Oliveira, 2022), including in the workplace (Andersen et al., 2011), this study support the idea that pursuing a healthy lifestyle through increased LTPA levels may prevent job stress-related headache disorders, or countervail domain-specific, job stress-related burden in the population with migraine and TTH.

Tailored interventions in the workplace could help reduce the headache burden and job domain-specific stress. These interventions should encompass a comprehensive set of behavioral interventions with both physical and mental health approaches to improve the work environment and well-being of individuals dealing with migraine and TTH. Additionally, our data suggest that improving workplace environment and granting workers more control may promote a more active lifestyle and its anti-inflammatory, health-enhancing effects in general, as well as headache-specific preventive mechanisms.

4.4. Strengths and limitations

The study's strengths include a large sample size of current workers with laboratory data and comprehensive models to consider confounder factors that could affect the results, such as anxiety or depression, medication use, and major chronic diseases.

The main limitation is the cross-sectional feature of the ELSA-Brasil baseline data. Our findings cannot rule out reverse causality across the associations between variables investigated, and more studies are needed to unveil the complex relationship between headache disorders, job stress, physical activity, and related putative biomarkers. The sociodemographic characteristics of our sample carry along another limitation. The ELSA-Brasil participants have higher education and socioeconomic status than the general Brazilian population, potentially causing selection bias and limiting the generalizability of the findings. However, the cohort includes a spectrum of socioeconomic groups that allows to identify sociodemographic impact on the results. The data on job stress, physical activity levels and mental disorders diagnoses relied on self-reporting data, which may introduce recall bias and social desirability bias.

5. Conclusions

LTPA positively influenced the job stress-headache disorders link in the ELSA-Brasil study, beyond age, sex, and mental health comorbidities factors, and potentially implicating GlycA in the job stress-TTH link. This finding unravels an interplay with potential clinical and epidemiological implications. Further occupational studies, utilizing more robust tools to gauge physical activity behavior, exploring possible headache-specific immune biomarkers, and investigating the impact of lifestyle and behavioral interventions focused on physical activity and stress management, will enhance the comprehension of these conditions. The higher prevalence of TTH and its relationship with job stress merits additional investigation to clarify the influence of lifestyle and interactions with putative immune biomarkers. Improved workplace conditions, and the promotion of a physically active lifestyle and stress management should be prioritized for reducing job stress and headache burden.

CRediT authorship contribution statement

Arão Belitardo de Oliveira: Writing – review & editing, Writing – original draft, Methodology, Formal analysis, Conceptualization. **Henrik Winter Schytz:** Writing – review & editing, Writing – original draft, Supervision, Conceptualization. **Mario Fernando Prieto Peres:** Writing – review & editing, Supervision, Conceptualization. **Juliane Prieto Peres Mercante:** Writing – review & editing, Conceptualization. **André R Brunoni:** Writing – review & editing, Supervision, Conceptualization. **Yuan-Pang Wang:** Writing – review & editing, Supervision, Conceptualization. **Maria del Carmen B. Molina:** Writing – review & editing, Supervision, Conceptualization. **Lucas Koji Uchiyama:** Writing – review & editing, Project administration, Conceptualization. **Paulo A. Lotufo:** Writing – review & editing, Supervision, Project administration, Funding acquisition. **Rigmor Højland Jensen:** Writing – review & editing, Supervision, Conceptualization. **Isabela M. Benseñor:** Writing – review & editing, Supervision, Project administration, Funding acquisition, Conceptualization. **Rosane Härter Griep:** Writing – review & editing, Supervision, Methodology, Conceptualization. **Alessandra C. Goulart:** Writing – review & editing, Supervision, Project administration, Methodology, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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Appendix A. Supplementary data

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