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Original

Headache, migraine, cutaneous allodynia, and mental health symptoms among Brazilian medical students: a cross-sectional study

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Abstract

Objective
To estimate the prevalence of headache and migraine among medical students in Brazil and analyze associations between headache burden, disability, cutaneous allodynia, depressive/anxiety symptoms, and hormonal factors.

Methods
This cross-sectional study included 135 medical students from UNIFIPA/FAMECA, surveyed via self-administered electronic questionnaire (October 2024-March 2025). Headache was classified per ICHD-3 criteria; disability, impact, allodynia, and depressive/anxiety symptoms were assessed using validated Brazilian-Portuguese MIDAS, HIT-6, ASC-12, BDI-I, and BAI.

Results
Mean age was 21.9 (±2.03) years. Recurrent headache was reported by 54.8% (n=74/135; 95% CI 46.0-63.4%), with higher odds in females than males (62.2% *vs.* 43.4% ; p=0.032, OR = 2.15, 95% CI 1.06-4.33). Migraine spectrum disorders accounted for 81.1% (n=60/74), probable migraine being most frequent. Depressive and anxiety symptom severities did not differ significantly between participants with and without headache (p=0.563 and p=0.484, respectively). Females showed higher depressive (p=0.019) and anxiety symptom severity (p<0.001). Cutaneous allodynia was strongly associated with severe functional impact (p<0.001) and disability (p=0.005). Among symptomatic females (n=51), 51.0% (n=26) reported a perimenstrual relationship, and 75.5% (n=40/53) reported Premenstrual Syndrome (PMS). Five of six women with migraine with aura (83.3%) used combined hormonal contraceptives.

Conclusions
Headache disorders, particularly migraine spectrum disorders, were highly prevalent among medical students. Female sex, cutaneous allodynia, and depressive/anxiety symptoms were relevant markers of burden. Combined hormonal contraceptive use among most women with migraine with aura highlights a gap in headache-informed counseling, reinforcing the need for systematic screening, mental health support, and safety education in university health services.

Keywords:
Migraine
Depression
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Anxiety
Sex

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Introduction

Headache disorders rank among the most prevalent and disabling neurological conditions worldwide, posing a growing challenge to public health systems. According to the Global Burden of Disease (GBD) Study 2023, approximately 2.9 billion individuals were affected by headache disorders that year, representing an age-standardized global prevalence of 34.6%. These indicators position this condition as the sixth most disabling group of diseases globally, with a rate of years lived with disability (YLD) of 541.9 per 100,000 inhabitants (1). Although tension-type headache (TTH) exhibits a prevalence nearly twice that of migraine, the latter accounts for the majority of the clinical burden within the group, representing approximately 90% of the YLDs attributed to headache disorders. Individually, migraine accounted for approximately 40.9 million YLDs globally in 2023, reflecting a disproportionate impact on the quality of life, productivity, and functioning of affected individuals (1).

Beyond individual suffering, headaches impose a significant socioeconomic burden. The World Health Organization (2024) recognizes this condition as a global priority, given that costs related to absenteeism, presenteeism, and high healthcare resource consumption total billions of dollars annually. In academic and professional contexts, performance impairment is particularly severe, hindering individuals' trajectories during critical stages of technical training and development (2). In this scenario, medical students emerge as a group of notable biological and mental health vulnerability. Literature demonstrates that the nature of medical training involves high levels of academic stressors, associated with a prevalence of depressive symptoms of approximately 27.2% and a notable frequency of suicidal ideation within this population (3,4). These psychological factors closely interact with pain processing; recent evidence suggests a complex relationship where psychological distress and migraine burden frequently co-occur and influence one another (5).

The vulnerability of this group is corroborated by investigations across diverse global jurisdictions. Studies conducted in Nigeria, Kuwait, and Egypt consistently confirm that the prevalence of migraine among medical students significantly exceeds that of the general population (6–8). In Asia, research in China and India highlights how environmental triggers inherent to medical education—such as chronic sleep deprivation and academic stress—directly modulate the pain experience (9,10). More recently, investigations in Saudi Arabia have pointed to a critical association between contemporary lifestyle factors, such as excessive electronic device use and sedentary behavior, and the worsening of headache episodes (11).

Despite the robustness of international data, critical gaps remain in systematic investigations within Brazilian medical education contexts. Regional studies in Brazil have quantified functional impact using validated instruments such as the HIT-6 (12) and MIDAS (13), demonstrating high levels of disability among medical students (14), as well as specific behavioral trigger-avoidance strategies (15). However, few analyses integrate clinical pain phenotyping with surrogate markers of central sensitization—such as cutaneous allodynia, which reflects trigeminovascular hyperexcitability in the brainstem and thalamus (16) and predicts severe disability and disease progression (17). Furthermore, despite the marked female preponderance in migraine, the interplay between female hormonal fluctuations, menstrual triggers, and the pharmacological safety of hormonal contraceptive use remains underreported in highly stressed student populations. Consequently, the lack of integrative studies assessing sensory, mental health symptoms, lifestyle, and hormonal factors prevents a comprehensive understanding of headache burden among Brazilian medical students.

Therefore, this study aimed to assess the prevalence and ICHD-3 diagnostic distribution of headache disorders among medical students at a private Brazilian medical school, and to evaluate the association between headache presence and depressive and anxiety symptom severity. Secondary objectives included evaluating the associations between headache presence or burden and headache-related functional impact and disability; the presence and severity of cutaneous allodynia; lifestyle-related factors such as physical activity frequency and Body Mass Index categories; sex differences; and female-specific hormonal factors, including perimenstrual attack patterns and Premenstrual Syndrome.

Methods

Study design and population

This is a cross-sectional, descriptive, and observational study conducted among medical students at the Catanduva Medical School (**UNIFIPA/FAMECA**), São Paulo, Brazil. Data collection took place between October 15, 2024, and March 29, 2025. The study was conducted in accordance with the ethical principles of the Declaration of Helsinki and followed the Strengthening of the Reporting of Observational Studies in Epidemiology (**STROBE**) guidelines (18).

Sampling and eligibility criteria

All regularly enrolled medical students across all academic years (1st to 6th year) at the Padre Albino University Center (UNIFIPA/FAMECA) represented the total eligible study population (N=600). Recruitment procedures were standardized and identical across all six academic years, utilizing electronic survey links hosted on Google Forms and distributed through official class communications and student representatives between October 15, 2024, and March 29, 2025. A non-probability convenience sampling method was employed. Out of 600 eligible students, 135 completed the survey, yielding an overall response rate of

22.5%. Inclusion criteria were: (1) medical students aged 18 years or older and (2) active enrollment in the medical program. Exclusion criteria were restricted to incomplete questionnaires and failure to provide digital informed consent. To prevent item-level missing data, the electronic platform was configured with mandatory response fields for all core clinical items. No a priori sample size or statistical power calculation was performed due to the convenience sampling design; instead, all valid responses obtained during the predefined data collection window were included.

Outcomes

The primary outcomes were the prevalence of headache disorders and their classification according to the International Classification of Headache Disorders Third Edition (ICHD-3) criteria (19), and the association between headache presence and depressive and anxiety symptom severity, as measured by the Beck Depression Inventory (BDI-I) and the Beck Anxiety Inventory (BAI) (20,21). Secondary outcomes comprised: (1) clinical headache profile, including age at headache onset and disease duration (years since onset, calculated as current age minus age at onset); (2) headache-related functional impact and disability, assessed by the Headache Impact Test (HIT-6) and the Migraine Disability Assessment Scale (MIDAS); (3) the presence and severity of cutaneous allodynia, determined by the Allodynia Symptom Checklist (ASC-12) (22); (4) lifestyle-related factors, including physical activity frequency and Body Mass Index (BMI) categories, and their associations with headache burden; and (5) female-specific hormonal factors, including the temporal relationship between headache attacks and the menstrual cycle, and the prevalence of Premenstrual Syndrome (PMS) among symptomatic participants.

Data collection instruments

The assessment tool consisted of a structured self-administered questionnaire comprising 125 items, covering sociodemographic variables, lifestyle habits, comorbidities, and clinical headache features.

Headache presence and clinical features were evaluated using a structured electronic questionnaire based on International Classification of Headache Disorders, 3rd edition (ICHD-3) criteria. Active headache status was evaluated within a 3-month recall period to estimate headache prevalence. The instrument specifically assessed age at onset, pain quality (pulsatile vs. non-pulsatile), attack duration (>4 hours unmedicated or <2 hours medicated), monthly attack frequency categories (1–7, 8–14, and ≥15 days/month), and accompanying symptoms, including nausea/vomiting, photophobia, phonophobia, and aura symptoms lasting >5 minutes (visual, sensory, or speech disturbances). Primary headache subtypes were operationalized through a diagnostic decision-tree algorithm: participants fulfilling all required ICHD-3 criteria for a specific primary headache were assigned definitive diagnoses, whereas those fulfilling all criteria except one were classified under probable categories, specifically Probable Migraine (ICHD-3 code 1.5.1). In cases of competing clinical features, diagnoses were hierarchically prioritized according to ICHD-3 guidelines, assigning a single primary headache diagnosis reflecting the predominant attack profile. To ensure diagnostic accuracy, all electronic survey outputs and algorithm classifications were individually reviewed and validated by a board-certified neurologist specializing in headache medicine (E.M.M.). Functional impact and mental health symptoms were assessed using Brazilian-Portuguese validated versions of the following scales: Headache Impact Test (HIT-6), Migraine Disability Assessment (MIDAS), Allodynia Symptom Checklist (ASC-12), Beck Depression Inventory (BDI-I) and Beck Anxiety Inventory (BAI).

Statistical analysis

Data were analyzed using JAMOVI software (**v.2.6.44**) (23). Descriptive analysis included means and standard deviations for continuous variables and absolute/relative frequencies for categorical variables. Differences between groups (headache vs. non-headache) for categorical variables were assessed using Pearson's Chi-square test, with Cramér's V reported as effect size, and Student's t-test (with Cohen's d) was applied for continuous variables. Associations between categorical variables across multiple groups, including sex versus depression and anxiety symptom severity, cutaneous allodynia versus functional impact (HIT-6) and disability (MIDAS), and sex versus allodynia presence, were also evaluated using Pearson's Chi-square test; when significant, post-hoc analysis was performed using standardized residuals (z-scores) to identify which cells drove the overall association. To compare disease duration across anxiety symptoms severity, the Kruskal-Wallis test was used, given the nonparametric distribution of the data, followed by Dwass-Steel-Critchlow-Fligner post hoc pairwise comparisons. To address potential confounding inherent to unadjusted bivariate comparisons, effect sizes and 95% confidence intervals were consistently reported to aid clinical interpretation; the absence of multivariable regression modeling was formally acknowledged as a study limitation. A significance level of $p<0.05$ was adopted for all analyses. The study was approved by the Institutional Review Board (CEP/FAMECA) under protocol No. 7.271.415. All volunteers provided digital informed consent prior to data collection.

Results

Participant characteristics and lifestyle

The study sample comprised 135 medical students, 82 women

and 53 men, with an overall mean age of 21.9 (±2.03) years. No statistically significant age difference was observed between participants with headache (22.1±2.03 years) and headache-free controls (21.6 ± 2.02 years; $t(133) = -1.36$, $p=0.177$, Cohen's d = -0.235). Females represented 60.7% (n=82) of the total population and exhibited significantly higher odds of reporting headache disorders compared to males (62.2% vs. 43.4%; $X^2(1) = 4.59$, p = 0.032; OR = 2.15, 95% CI: 1.06–4.33; Cramer's V = 0.184). Regarding lifestyle characteristics, 78.5% (n=106) engaged in regular physical activity (≥3 times/week), 16.3% (n=22) were smokers, and 27.4% (n=37) were classified as overweight or obese. Bivariate analyses demonstrated no statistically significant associations between headache presence and physical activity (75.6% in headache group vs. 82.0% in controls; OR=1.46, 95% CI: 0.63–3.39; $p=0.376$), smoking (13.5% vs. 19.7%; OR=0.64, 95% CI: 0.26–1.60; $p=0.335$), or elevated BMI (29.7% vs. 24.6%; OR=1.30, 95% CI: 0.60–2.79; $p=0.505$) (Table 1).

Table 1. Sociodemographic characteristics, lifestyle factors, and headache classification according to ICHD-3 criteria among medical students (N=135)

Variable	Total (N=135)	With Headache (n=74)	Without Headache (n=61)	*p*-value	Cramer's V
Age (Mean (SD))	21.9 (±2.03)	22.1 (±2.03)	21.6 (±2.02)	0.177*	-
Sex, n (%)				0.032	0.184
Female	82 (60.7%)	51 (68.9%)	31 (50.8%)	-	-
Male	53 (39.3%)	23 (31.1%)	30 (49.2%)	-	-
BMI, n (%)				0.505	0.057
Normal Weight	98 (72.6%)	52 (70.3%)	46 (75.4%)	-	-
Overweight/Obesity	37 (27.4%)	22 (29.7%)	15 (24.6%)	-	-
Physical activity, n (%)				0.376	0.076
Regular (≥3x/week)	106 (78.5%)	56 (75.6%)	50 (82.0%)	-	-
Irregular (<3x/week)	29 (21.5%)	18 (24.4%)	11 (18.0%)	-	-
Smoking, n (%)				0.335	0.083
No	113 (83.7%)	64 (86.5%)	49 (80.3%)	-	-
Yes	22 (16.3%)	10 (13.5%)	12 (19.7%)	-	-
Headache classification (ICHD-3)			**n (% of headache group)**		
Probable migraine	-	30 (40.5%)	-	-	-
Migraine without aura	-	22 (29.7%)	-	-	-
Migraine with aura	-	8 (10.8%)	-	-	-
Tension-type headache	-	14 (18.9%)	-	-	-

SD: Standard Deviation; **CI:** Confidence Interval; **OR:** Odds Ratio; **Mean Diff.:** Mean Difference; **BMI:** Body Mass Index; **ICHD-3:** International Classification of Headache Disorders, 3rd edition; **Ref.:** Reference category.
*Calculated using Student's t-test for independent samples ($t = -1.36$, $df = 133$). Reported measure of effect for Age is the Mean Difference (Group 'With Headache' minus Group 'Without Headache') with its 95% CI, and effect size is represented by Cohen's d (d = -0.235). All categorical variables were analyzed using Pearson's chi-square test (X^2), reporting Odds Ratio (95% CI) and Cramér's V.

Headache characteristics and classification

Of the 135 evaluated medical students, the 3-month prevalence of recurrent headaches was 54.8% (n=74/135; 95% CI: 46.0%–63.4%). Among symptomatic individuals, the mean age at headache onset was 13.7 (±4.27) years, as reported by 60 participants who recalled their age at onset. Clinical classification according to ICHD-3 criteria demonstrated a marked predominance of migraine spectrum disorders, which accounted for 81.1% (n=60/74; 95% CI: 70.3%–89.3%) of all symptomatic cases. Within the migraine spectrum, Probable Migraine was the most prevalent diagnostic subtype (40.5%, n=30/74; 95% CI: 29.3%–52.6%), followed by Migraine without Aura (29.7%, n=22/74; 95% CI: 19.7%–41.5%) and Migraine with Aura (10.8%, n=8/74; 95% CI: 4.8%–20.2%). Tension-type headache was identified in 18.9% (n = 14/74; 95% CI: 10.8%–29.7%) of symptomatic participants (Table 1).

Mental health symptoms: depressive and anxiety

Depressive and anxiety symptom severities were evaluated across the entire study cohort (N=135) using the Beck Depression Inventory (BDI-I) and Beck Anxiety Inventory (BAI) (Table 2). When stratified by headache status, no statistically significant differences were observed between participants with and without headache regarding depressive symptoms severity ($X^2(3) = 2.05$, p=0.563; Fisher's exact test p = 0.580; Cramér's V=0.123) or anxiety symptoms severity ($X^2(3) = 2.45$, p=0.484; Fisher's exact test p=0.472; Cramér's V=0.135). Severe depressive symptoms were identified in 20.3% (15/74) of students with headache compared to 16.4% (10/61) of controls, whereas severe anxiety symptoms were reported by 2.7% (2/74) and 3.3% (2/61), respectively.

Table 2. Distribution of depressive and anxiety symptom severity by headache status and gender among medical students (N=135)

Classification	With Headache (n=74) n (%)	Without Headache (n=61) n (%)	Total (n=135) n (%)	p-value (Headache)	Cramer's V (Headache)	Female (n=82) n (%)	Male (n=53) n (%)	p-value (Sex)	Cramer's (Sex)
Depression Severity (BDI)									
Minimal	24 (32.4%)	26 (42.6%)	50 (37.0%)	0.563	0.123	24 (29.3%)	26 (49.1%)	0.019	0.272
Mild	22 (29.7%)	18 (29.5%)	40 (29.6%)			23 (28.0%)	17 (32.1%)		
Moderate	13 (17.6%)	7 (11.5%)	20 (14.8%)			14 (17.1%)	6 (11.3%)		
Severe	15 (20.3%)	10 (16.4%)	25 (18.5%)			21 (25.6%)	4 (7.5%)		
Anxiety Severity (BAI)									
Minimal	42 (56.8%)	42 (68.9%)	84 (62.2%)	0.484	0.135	41 (50.0%)	43 (81.1%)	< .001	0.355
Mild	19 (25.7%)	10 (16.4%)	29 (21.5%)			20 (24.4%)	9 (17.0%)		
Moderate	11 (14.9%)	7 (11.5%)	18 (13.3%)			17 (20.7%)	1 (1.9%)		
Severe	2 (2.7%)	2 (3.3%)	4 (3.0%)			4 (4.9%)	0 (0.0%)		

BDI: Beck Depression Inventory; **BAI:** Beck Anxiety Inventory; **CI:** Confidence Interval.
*Calculated using Pearson's chi-square test (X^2). Cramer's V reflects the effect size for categorical variables across tables larger than 2x2 (conventionally interpreted as: 0.10 = small effect, 0.30 = moderate effect, 0.50 = large effect).

Conversely, depressive and anxious symptom severity was strongly associated with sex. Female medical students demonstrated significantly higher severity of depressive symptoms ($X^2(3) = 9.97$, p=0.019; Fisher's exact test p=0.017; Cramér's V=0.272), with 25.6% (21/82) reporting severe depressive symptoms compared to 7.5% (4/53) of males. Similarly, anxiety symptoms severity was markedly higher in females ($X^2(3) = 17.0$, p<0.001; Fisher's exact test p<0.001; Cramér's V = 0.355). Moderate-to-severe anxiety symptoms were present in 25.6% (21/82) of female students, whereas only 1.9% (1/53) of male students reached moderate anxiety symptoms and none experienced severe anxiety symptoms (Table 2).

Among symptomatic participants with valid disease duration data (n=63), headache duration significantly differed across anxiety symptoms severity (Kruskal-Wallis $X^2(3) = 14.2$, p=0.003, ε^2=0.229). Post-hoc pairwise comparisons using the Dwass-Steel-Critchlow-Fligner test confirmed that participants with moderate anxiety exhibited significantly longer disease duration compared to those with minimal (W=-4.131, p=0.018) or mild anxiety (W=-3.919, p=0.029).

Allodynia and functional impact

Cutaneous allodynia (CA), assessed via the ASC-12 ques-

tionnaire among verified headache cases (n=74), was strongly associated with both functional impact (HIT-6) and headache-related disability (MIDAS). Regarding functional impact, valid HIT-6 responses were available for 76 participants (comprising all 74 symptomatic students and 2 headache-free controls who completed this block). A statistically significant association was observed across CA severity categories and HIT-6 grades ($X^2(9) = 27.3$, p=0.001; Fisher's exact test p<0.001; Cramér's V = 0.346). Among participants with moderate allodynia (n=8), 75.0% (6/8; 95% CI: 34.9%–96.8%) were concentrated in the substantial (37.5%, 3/8) or severe (37.5%, 3/8) impact categories. In contrast, among non-allodynic participants (n=51), only 11.8% (6/51; 95% CI: 4.4%–23.9%) reported substantial

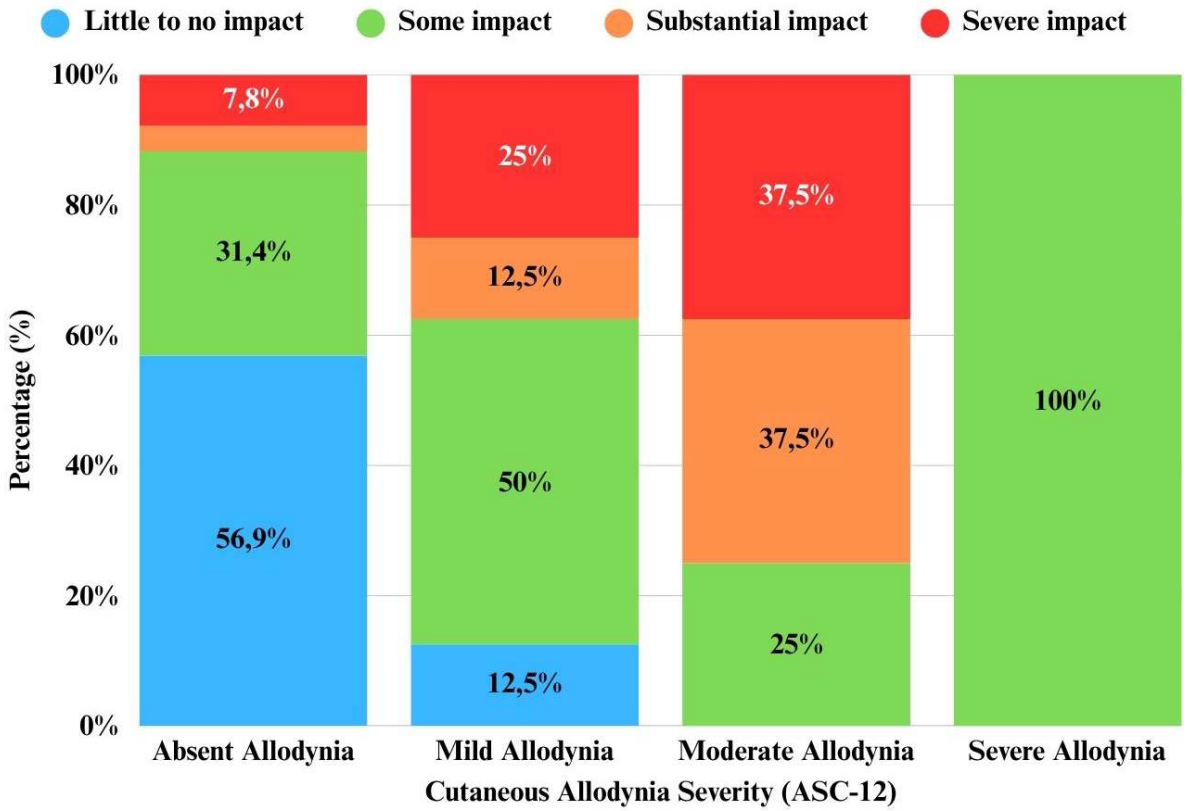

Figure 1. Headache-related functional impact stratified by cutaneous allodynia severity. Functional impact levels assessed using the HIT-6 questionnaire stratified by cutaneous allodynia severity (ASC-12) among medical students with headache (n=76). Subgroup sample sizes are as follows: absent allodynia (n=51), mild allodynia (n=16), moderate allodynia (n=8), and severe allodynia (n=1). Percentages within stacked bars represent relative proportions within each allodynia category. Statistical association was evaluated using Pearson's Chi-square ($X^2(9)=27.3$, $p=0.001$) and Fisher's exact test ($p<0.001$), with a Cramér's V effect size of 0.346.

or severe functional impact, with the majority experiencing little-to-no impact (56.9%, 29/51) (Figure 1).

For headache-related disability measured by the MIDAS scale, complete data were available for 71 of the 74 symptomatic participants, as 3 respondents submitted incomplete questionnaires and were excluded from this specific analysis. A consistent relationship was identified between allodynia and disability ($X^2(9)=24.1$, $p=0.004$; Fisher's exact test $p= 0.005$; Cramér's V=0.337). Severe disability (MIDAS Grade IV) was present in 85.7% (6/7; 95% CI: 42.1%–99.6%) of students with moderate allodynia (n=7), compared to only 17.0% (8/47; 95% CI: 8.1%–30.0%) among non-allodynic respondents (Figure 2).

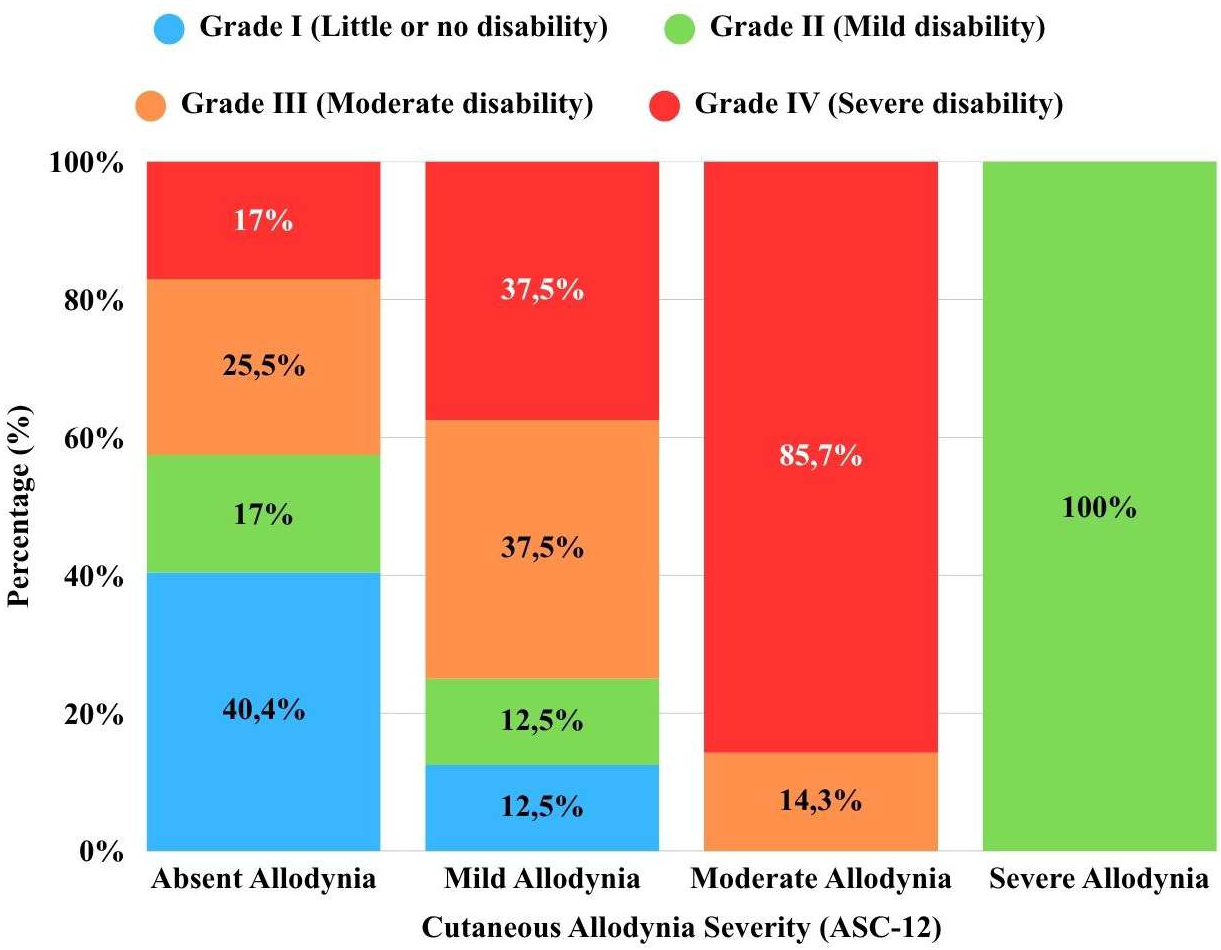

Figure 2. Headache-related clinical disability stratified by cutaneous allodynia severity. Disability grades were assessed by the Migraine Disability Assessment Scale (MIDAS), and cutaneous allodynia severity was categorized using the 12-item Allodynia Symptom Checklist (ASC-12) among medical students with active headache (n=71). Subgroup sample sizes are as follows: absent allodynia (n=47), mild allodynia (n=16), moderate allodynia (n=7), and severe allodynia (n=1). Percentages within stacked bars represent relative proportions within each allodynia category. Statistical association was evaluated using Pearson's Chi-square ($X_2(9)=24.1$, $p=0.004$) and Fisher's exact test ($p=0.005$), with a Cramér's V effect size of 0.337.

Female-specific and hormonal factors

Female students represented 60.7% (n=82/135) of the total population, of whom 51 were diagnosed with active headache disorders. Among these symptomatic females (n=51), headaches demonstrated a distinct temporal relationship with the menstrual cycle, with 51.0% (n=26/51; 95% CI: 37.6%–64.2%) reporting either triggering or exacerbation of symptoms in the perimenstrual period. This occurrence was evenly distributed across ICHD-3 subtypes ($p=0.617$, Fisher's exact test). Analysis of current hormonal contraceptive use among the 51 women with headache revealed no statistical association with specific ICHD-3 diagnostic subtypes ($X^2(3) = 1.64$, $p=0.650$; Fisher's exact test $p=0.705$; Cramér's V=0.179). A clinically critical pattern emerged within the migraine with aura subgroup (n=8 total; 6 females, 2 males): among the 6 female participants, 5 (83.3%, n=5/6) reported current use of combined hormonal contraceptives.

Valid data regarding Premenstrual Syndrome (PMS) symptoms and overall combined hormonal contraceptive prevalence was available for only a subset of 53 women, revealing a high descriptive prevalence of both PMS symptoms (75.5%, n=40/53) and current contraceptive use (73.6%, n=39/53) within this group. No further statistical comparison by headache status was performed for these specific variables due to the low response rate among asymptomatic individuals.

Discussion

More than half of the participants reported experiencing recurrent headaches, a finding consistent with the growing evidence highlighting an elevated prevalence of headache disorders among medical students (24). This pattern may be largely attributed to the mentally demanding characteristics of medical training, including chronic sleep deprivation, high academic pressure, and the emotional burden inherent to clinical education. Among symptomatic individuals, migraine spectrum disorders were predominant. Although literature broadly describes tension-type headache (TTH) as the most prevalent primary headache in young adults, this discrepancy likely reflects a combination of selection bias, questionnaire design, and diagnostic algorithm characteristics rather than a true epidemiological inconsistency. First, self-selection bias may have encouraged students with more frequent or disabling headaches to complete the survey, while those with mild, non-disabling TTH were less likely to participate. Second, self-administered questionnaires based on ICHD-3 criteria demonstrate higher sensitivity for capturing migrainous features (such as pulsatility, nausea, and photo/phonophobia) but lack the physical examination component (pericranial muscle tenderness) needed to fully characterize TTH (19,25). Finally, the diagnostic algorithm categorized borderline cases endorsing prominent migrainous features as probable migraine whenever all but one formal criterion was met. Together, these methodological factors explain the relative underrepresentation of TTH and the higher proportion of migraine spectrum disorders in self-reported university cohorts compared to clinical settings (25).

According to literature published by the *European Journal of Neurology* (26), migraine exhibits higher prevalence and significant clinical impairment in female participants, a pattern widely described in epidemiological studies. This female preponderance may be related, among other factors, to the modulatory role of estrogen on nociceptive pathways, rendering women particularly susceptible to migraine across reproductive years. Notably, the mean age of headache onset observed predates university enrollment by nearly a decade, suggesting that the academic environment does not initiate the condition but rather amplifies a pre-existing vulnerability (27). The convergence of early biological onset and female predominance points to a strong hormonal and genetic substrate underlying migraine in this population.

Studies have established an association between pain and depressive states (28), where individuals with chronic pain consistently present higher depression scores compared to pain-free counterparts. In our sample, however, depressive and anxiety symptom severity did not differ significantly between medical students with and without headache. Although severe depressive symptoms presented a higher numerical frequency in the headache group, this absence of significant difference indicates that mental health symptoms are widespread across medical students regardless of headache status, though statistical power constraints to detect subtle effect sizes must also be considered. Importantly, sex was strongly associated with both depressive and anxiety burden: females were concentrated in the severe depressive and moderate anxiety symptoms categories, while males predominantly presented minimal symptoms of both conditions. This dimorphism is consistent with literature describing heightened stress reactivity and greater affective vulnerability in women with migraine (29). Furthermore, participants with moderate anxiety symptoms exhibited significantly longer disease duration, reflecting an association between pain and emotional burden. When interpreting these findings, it is noteworthy that the Beck Anxiety Inventory (BAI) primarily emphasizes somatic manifestations of anxiety. Future investigations in medical student populations would benefit from incorporating instruments such as the Generalized Anxiety Disorder-7 (GAD-7), which places greater emphasis on cognitive dimensions, like excessive and uncontrollable worry. Capturing both somatic and cognitive domains may provide a more comprehensive characterization of psychological distress and further clarify its synergistic interplay with headache burden.

Previous studies describe greater susceptibility in women to central sensitization mechanisms in the presence of allodynia, driven by hormonal influences on pain modulation and excitability of nociceptive pathways (30). Consistently, a marked sex dimorphism in cutaneous allodynia (CA) was observed in our cohort, being substantially more frequent in female participants. Beyond its sex-based distribution, allodynia was strongly associated with clinical burden: higher allodynia intensity correlated with substantial or severe functional impact and disability on the HIT-6 and MIDAS scales, whereas non-allodynic participants experienced minimal impairment. This gradient reflects the underlying pathophysiology of central sensitization, characterized by amplified neuronal responsiveness to ordinarily non-painful stimuli, leading to intensified pain perception and prolonged attacks (31). As a clinical marker of central sensitization, allodynia may reflect a heightened trigeminovascular excitability, capturing a dimension of pain processing that extends beyond attack frequency alone.

Regarding lifestyle characteristics, no statistically significant associations were identified between headache presence or disability and Body Mass Index (BMI) categories, physical activity, or smoking. Rates of severe disability were comparable across BMI groups, suggesting that adiposity alone does not drive functional burden in this sample. These findings diverge from the literature describing pathophysiological mechanisms, such as chronic systemic inflammation, alterations in the leptin-dopamine axis, and insulin resistance, linking obesity, sedentary behavior, and smoking to altered pain modulation and heightened neuronal

excitability (32,33). These null associations likely reflect several methodological and epidemiological factors. First, the study population exhibits relatively homogeneous characteristics typical of a young university cohort, including a high baseline engagement in physical activity, which may have reduced subgroup variance. Second, lifestyle variables were evaluated through broad categorical classifications rather than continuous quantitative tools, limiting the ability to capture subtle dose-response relationships. Third, the limited sample size provided restricted statistical power to detect modest effect sizes. Furthermore, associations between lifestyle or metabolic factors and headache burden are more consistently observed in chronic daily headache populations rather than in episodic profiles such as those characterizing our cohort (34). Nonetheless, early lifestyle modification remains clinically relevant, as it contributes to overall student well-being and the long-term prevention of headache chronification (35).

Migraine attacks frequently exhibit a perimenstrual association, occurring preferentially around the onset of menstrual flow and exhibiting greater pain intensity and treatment resistance compared to non-menstrual episodes (36). In the present study, approximately half of the female participants reported a perimenstrual relationship with headaches, and Premenstrual Syndrome was frequently reported. Although no statistically significant association was found between PMS and headache presence, the high prevalence of perimenstrual headache reporting reinforces hormonal fluctuations as critical triggers. Of particular clinical concern, five of the six female participants diagnosed with Migraine with Aura (83.3%) reported current use of combined hormonal contraceptives, a combination formally contraindicated due to the substantially increased risk of ischemic stroke. This high rate of contraindicated use aligns with recent observational data: a large UK population database study of 142,867 women with migraine with aura revealed that 15% continued using combined oral contraceptives even after diagnosis (37), while a US chart review of 7,451 patients demonstrated similar rates of combined contraceptive use between women with and without aura (~20%) (38). The reported use of combined hormonal contraceptives among female participants classified as having migraine with aura raises an important safety concern, highlighting the need for clinical evaluation and improved awareness regarding contraceptive eligibility guidelines (39).

Limitations

The present study has limitations that must be considered. The cross-sectional design does not allow for establishing causality between variables, such as mood disorders and headaches. Convenience sampling via an electronic self-administered questionnaire may have introduced selection bias, as students with headaches or higher academic engagement might be more likely to respond. The questionnaire did contain records of the specific academic year of medical training for each participant. Although recruitment procedures were identical and distributed uniformly across all six classes, the lack of disaggregated data by academic year precludes stratified analyses across training stages and represents a potential source of unmeasured selection bias. While widely used, self-applied instruments are subject to recall bias; to minimize this, participants were instructed to report only symptoms from the last three months. Additionally, the overall sample size of 135 participants is smaller than international reference studies, limiting statistical power in subgroup analyses, particularly for those with lower representation, such as migraine with aura. The absence of an in-person clinical interview conducted by a neurologist may also have resulted in less precise diagnostic classifications than those obtained through semi-structured interview protocols.

Regarding specific subgroup analyses, allodynia data were available for only 76 of the 135 participants and MIDAS disability scores were available for only 71 participants who provided complete answers, which limits the representativeness and statistical power of the functional impact findings. The hormonal analysis was constrained by the very limited number of headache-free females available for comparison, precluding robust conclusions about the association between PMS and headache presence. Similarly, the Migraine with Aura subgroup comprised only eight participants; although the pharmacological finding regarding combined hormonal contraceptive use is clinically significant, its generalizability requires confirmation in larger cohorts.

Furthermore, all statistical analyses conducted in this study were essentially bivariate. Given the sample size constraints within specific clinical subgroups (such as participants with migraine with aura or valid allodynia scores), multivariable regression models were not performed to avoid model overfitting and unstable parameter estimates. Consequently, the observed associations may be influenced by unmeasured potential confounding variables. To mitigate this limitation and facilitate clinical interpretation, effect size measures (Cramér's V, Cohen's d, and ε^2) and 95% confidence intervals were systematically reported alongside p-values.

In addition, the absence of screening for Medication Overuse Headache (MOH) represents a relevant gap, as this condition may act as a confounding factor in a population with ready access to analgesics. Finally, as a single-institution study conducted at a private medical school, the findings may not be fully generalized to public universities or institutions with distinct socioeconomic and academic profiles.

Conclusion

In conclusion, headache disorders—predominantly within the migraine spectrum—are highly prevalent among medical students, with female students exhibiting a significantly higher burden of

depressive and anxiety symptoms. Cutaneous allodynia was strongly associated with severe functional impact and disability, acting as a relevant marker of clinical burden. Furthermore, longer headache duration was significantly associated with greater anxiety symptom severity. The reported use of combined hormonal contraceptives among female participants classified as having migraine with aura raises an important safety concern, pointing to the need for systematic headache screening and improved awareness of contraceptive eligibility guidelines in university health services.

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