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Depression and Anxiety Symptoms in Primary Headache Disorders: A Cross-Sectional Study

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Abstract

Objectives: To investigate depression and anxiety symptoms in individuals with headache disorders (HD).

Methods: Consecutive individuals with headache attending a headache outpatient clinic interviewed with the Hamilton Rating Scale for Depression (HAM-D) and for Anxiety (HAM-A), along with age, sex, and education matched non-headache individuals.

Results: 2,673 individuals with headache (females 71.2%) and 464 non-headache individuals (females 70.9%) were interviewed (participation rates 98.3% and 91.0% respectively). Migraine was diagnosed in 49.7%, tension-type headache in 38%, cluster headache 5.2% and medication overuse MO in 21.8%. Participants with HD scored more in HAM-A (OR= 0.211, CI95%: 0.171-0.259, p<0,001) and HAM-D scales (OR= 0.431, CI95%: 0.352-0.529, p<0,001) than non-headache individuals. Participants with chronic HDs (≥15 days with headache for ≥3 consecutive months; 52.5%) scored higher for both HAM-A (OR= 1.944, CI95%: 1.640-2.303, p<0,001) and HAM-D (OR= 1.625, CI95%: 1.359-1.944, p<0,001) than those with episodic HDs (33.1%), as did participants with MO vs. participants without MO (OR= 3.418, CI95%: 2.655-4.399, p<0,001 for HAM-A, OR= 3.043, CI95%: 2.322-3.986, p<0,001 for HAM-D). Female, low-educated, and middle-aged participants scored higher on both scales.

Interpretation: Because symptoms of anxiety and depression are substantial in people with HD, treating physicians should look for them and manage them appropriately.

Keywords: Depression; Anxiety; Migraine; Tension type headache; Medication overuse headache; Cluster headache

Introduction

Both headache and depressive disorders are very prevalent and among the top 15 causes for disability across 369 diseases and injuries worldwide in year 2019 **[1].** Notably, the burden of the disorders increased the last 20 years markedly, within the young and productive age group of people, where both disorders are leading causes **[1].** Headache and depressive disorders are often co-exist in the some individual **[2,3],** multiplying the burden of both conditions and limiting the therapeutical outcome **[4].** Their association is undisputed. However, the mechanisms underlying the purported association are complex and the results of genetic studies have shown a bidirectional influence **[5].** In addition, anxiety and depression have been studied as potential co-factors for headache chronification, thus treating anxiety and/or depression has been suggested as a part of migraine management **[6].**

The aim of this cross-sectional study was to estimate the prevalence of anxiety and depression like symptoms in individuals with Headache Disorders (HDs) and to verify the potential association with specific headache disorder (migraine, tension-type headache, medication overuse).

Materials and Methods

Consecutive individuals with HDs, attending the Aeginition Headache outpatient clinic, were included in the study. For everyone, the main demographic features (age, sex, education), clinical headache features (disease duration, frequency, concurrent autonomic symptoms), provoking factors (alcohol, smoking, coffee), coexisting somatic and mental disorders and drug treatment were specifically investigated during history taking and recorded in a structured questionnaire. Moreover, all participants underwent a full physical and neurological examination and special interview with the Hamilton Anxiety Rating Scale (HAM-A) and Hamilton Depression Rating Scale (HAM-D). The HAM-A was one of the first rating scales developed to measure the severity of anxiety symptoms and is still widely used today in both clinical and research settings. The administration time takes 10–15 minutes. The scale consists of 14 items, each defined by a series of symptoms measuring mental and somatic symptoms and scored on a scale of 0 (not present) to 4 (severe), with a total score range of 0–56, where <17 indicates mild severity, 18–24 mild to moderate severity and 25–30 moderate to severe **[7].** The HAM-D is consisted of 17 items assessing both mental and somatic depressive symptoms on a scale of 0-4, with a total score range of 0-68, where 10-13 indicates mild depression; 14-17 mild to moderate; >17 moderate to severe depression **[8,9].** HD diagnosis was performed according to the ICHD-3beta **[10].** Age and sex matched control group was consisted of healthy individuals without any headache type. Additionally, participants were grouped by education at three levels (primary, secondary, and tertiary education). All participants singed special informed concept. The study protocol was approved by the Ethical Committee of the Aeginition Hospital (ADA: ΩΝΚΟ46Ψ8Ν2-2ΒΨ).

Statistics

Descriptive statistics were used to compare the main demographic and clinical characteristics and analysis of variance was used to compare mean values of continuous variables. An independent samples t-test was conducted to understand if there is a difference in anxiety symptoms that patients report in Hamilton Anxiety scale in episodic and chronic headaches (any headache type occurred for more than 15 days per month for more than 3 consecutive months). The t-test conducted was an independent t-test as the samples were independent and the variable headache type is a qualitative variable. Variances were found equal as p value was non-significant p>.05, so the homogeneity of variance assumed. A One-Way Between Subjects ANOVA test was conducted to investigate whether there was a difference between the patients from episodic migraine, chronic migraine, episodic Tension-Type Headache (TTH), chronic TTH, episodic cluster, chronic cluster, New Daily Persistent Headache (NDPH) and other types of headaches in relation to the severity of the anxiety symptoms that patients report. To compare the mean score in Hamilton anxiety scale on patients with headache and control group, an independent samples t-test was performed. The assumptions that were met for the conduction of this test include: the samples were independent and there was qualitative variable. To compare the score of anxiety symptoms scale for headache patients with medication overuse and those with no medication overuse an independent samples t-test was conducted. In all comparisons, the homogeneity of variances was tested with Levene's test.

Results

The study was performed between January 2018 and January 2021 and 2,673 consecutive individuals with HD (1,902 women, 71.2% and 771 men, 28.8%) and 464 headache-free participants were agreed to participate in the study and interviewed. The participation rates were 98.3% and 91.0%, respectively. Among participants with headache, 1,261 (47.2%) had chronic HDs and 1,412 (52.8%) episodic HDs. Migraine was diagnosed in 1,328 (49.7%), TTH in 1,015 (38%), cluster headache in 139 (5.2%) and Medication Overuse (MO) in 583 participants (21.8%).The demographic characteristics of participants by HD are presented in **Table 1.** The mean score for HAM-A and HAM-D in participants with HDs were 19.62±7.79 and 14.39±6.71, vs. 13.09±8.15 and 12.03±6.96 in participants without headaches, respectively (OR= 0.211, 95%CI: 0.171-0.259, p < 0.001 and 0.431, 95%CI: 0.352-0.529, p < 0.001, respectively). Participants with chronic HDs (52.5%) scored higher for both HAM-A (OR= 1.944, 95%CI: 1.640-2.303, p<0,001) and HAM-D (OR= 1.625, 95%CI: 1.359-1.944, p<0,001) than those with episodic HDs (33.1%), respectively **(Table 2 and 3, Figure 1 and 2).** More participants with HDs than non-headache participants were scored ≥13 or ≥25 in HAM-A and ≥7 or ≥13 in HMA-D, indicating that they were suffering from a mild or severe anxiety-like or depression-like condition, respectively **(Table 4).**

Table 1: Descriptive Statistics.

Headache Disorder	No of participants	Age Years (SD)	Male (%)	Female (%)	Primary Education	Secondary Education	Tertiary Education	Disease duration years (SD)
All	2.673	40.97	771	1,902	417	947	1307	24.25

		-12.12	-28.8	-71.2	-15.60%	-35.40%	-48.90%	-15.47
Migraine	1,328	41.04	253	1075	173	495	659	24.03
	-49.70%	-12	-19.1	-80.9	-13	-37.3	-49.7	-15.42
Episodic Migraine	886	41.55	174	712	98	320	467	24.54
	-33.20%	-12.38	-19.6	-80.4	-11.1	-36.2	-52.8	-14.87
Chronic Migraine	442	40	79	363	75	174	193	22.97
	-16.50%	-11.15	-17.9	-82.1	-17	-39.4	-43.7	-16.45
TTH	1,015	41.35	337	678	196	337	482	24.81
	-38%	-12.48	-33.2	-66.8	-19.3	-33.2	-47.5	(15.51
Episodic TTH	437	41.55	141	296	67	139	231	25.16
	-16.30%	-11.91	-32.3	-67.7	-15.3	-31.8	-52.9	-15.23
Chronic TTH	578	41.2	196	382	129	198	251	24.55
	-21.60%	-12.9	-33.9	-66.1	-22.3	-34.3	-43.4	-15.73
Cluster Headache	139	40.47	104	35	15	55	69	24.53
	-5.20%	-11.46	-74.8	-25.2	-10.8	-39.6	-49.6	-15.55
Episodic CH	89	39.56	71	18	10	36	43	22.91
	-3.30%	-11.31	-79.8	-20.2	-11.2	-40.4	-48.3	-14.91
Chronic CH	50	42.08	33	17	5	19	26	27.42
	-1.90%	-11.64	-66	-34	-10	-38	-52	-16.4
MO	583	43.78	110	473	144	204	234	27.02
	-21.80%	-13.12	-18.90%	-81.10%	-24.70%	-35%	-40.10%	-14.69
NDPH	35	37.4	14	21	3	12	20	18.85
	-1.30%	-8.96	-40	-60	-8.6	-34.3	-57.1	-16.22
Other HD	156	39.28	63	93	31	48	77	23.43
	-5.80%	-11.67	-40.4	-59.6	-19.9	-30.8	-49.4	-15.19
Headache Free participants	464	41.59	135	329	71	165	228	
		-14.62	-29.10%	-70.90%	-15.30%	-35.50%	-49.10%	

TTH: Tension-Type Headache; CH: Cluster Headache; MO: Medication Overuse; NDPH: New Daily Persistent Headache; HD: Headache Disorders.

Table 2: Mean scores of Hamilton scale for Anxiety by headache disorder (HD).

	Episodic Migraine (M=18.02, SD=7.2)	Chronic Migraine (M=22.77, SD=7.7)	Episodic TTH (M=18.52, SD=6.74)	Chronic TTH (M=22.54, SD=7.66)	Episodic CH (M=13.58, SD=6.96)	Chronic CH (M=12.94, SD=6.26)	NDPH (M=18.26, SD=7.26)	Other HD (M=17.3, SD=8.3)	Headache free population (M=13.09, SD=8.15)
Episodic Migraine (M=18.02, SD=7.2)	NA	p<0.001	NS	p<0.001	p<0.001	p<0.001	NS	NS	p<0.001
Chronic Migraine (M=22.77, SD=7.7)	p<0.001	NA	p<0.05	NS	p<0.001	p<0.001	p<0.05	p<0.05	p<0.001
Episodic TTH (M=18.52, SD=6.74)	NS	p<0.05	NA	p<0.001	p<0.001	p<0.001	NS	NS	p<0.001
Chronic TTH (M=22.54, SD=7.66)	p<0.001	NS	p<0.001	NA	p<0.001	p<0.001	p<0.05	p<0.001	p<0.001
Episodic CH (M=13.58, SD=6.96	p<0.001	p<0.001	p<0.001	p<0.001	NA	NS	p<0.05	p<0.001	NS

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Chronic CH (M=12.94, SD=6.26)	p<0.001	p<0.001	p<0.001	p<0.001	NS	NA	p<0.05	p<0.001	NS
NDPH (M=18.26, SD=7.26)	NS	p<0.05	NS	p<0.05	p<0.05	p<0.05	NA	NS	p<0.001
Other HD (M=17.3, SD=8.3)	NS	p<0.001	NS	p<0.001	p<0.001	p<0.001	NS	NA	p<0.001
Headache free population (M=13.09, SD=8.15)	p<0.001	p<0.001	p<0.001	p<0.001	NS	NS	p<0.001	p<0.001	NA

Table 3: Mean scores of Hamilton scale for Depression by headache disorder (HD).

	Episodic Migraine (M=13.42, SD=6.5)	Chronic Migraine (M=15.49, SD=6.75)	Episodic TTH (M=13.65, SD=6.06)	Chronic TTH (M=16.74, SD=6.57)	Episodic CH (M=11.40, SD=6.55)	Chronic CH (M=9.22, SD=5.67)	NDPH (M=12.97, SD=7.43)	Other HD (M=13.79, SD=7.19)	Headache free population (M=12.03, SD=6.96)
Episodic Migraine (M=13.42, SD=6.5)	NA	p<0.001	NS	p<0.001	NS	p<0.001	NS	NS	p<0.05

Chronic Migraine (M=15.49, SD=6.75)	p<0.001	NA	p<0.001	NS	p<0.001	p<0.001	NS	NS	p<0.001
Episodic TTH (M=13.65, SD=6.06)	NS	p<0.001	NA	p<0.001	NS	p<0.05	NS	NS	p<0.05
Chronic TTH (M=16.74, SD=6.57)	p<0.001	NS	p<0.001	NA	p<0.001	p<0.001	p<0.001	p<0.001	p<0.001
Episodic CH (M=11.40, SD=6.55)	NS	p<0.001	NS	p<0.001	NA	NS	NS	NS	NS
Chronic CH (M=9.22, SD=5.67)	p<0.001	p<0.001	p<0.05	p<0.001	NS	NA	NS	p<0.001	NS
NDPH (M=12.97, SD=7.43)	NS	NS	NS	p<0.001	NS	NS	NA	NS	NS
Other HD (M=13.79, SD=7.19)	NS	NS	NS	p<0.001	NS	p<0.001	NS	NA	NS
Headache Free participants (M=12.03, SD=6.96)	p<0.05	p<0.001	p<0.05	p<0.001	NS	NS	NS	NS	NA

Table 4: Participants with anxiety or depression like conditions by headache.

	Participants with headaches N (%)	Participants without headaches N (%)	OR	95% CI	P
HAM-A ≥13	1,973 (73.8)	173 (37.3)	0.211	0.171-0.259	<0.001

HAM-A ≥25	736 (27.5)	57 (12.3)	0.369	0.276-0.493	<0.001
HAM-D ≥7	2,006 (75.0)	262 (56.5)	0.431	0.325-0.529	<0.001
HAM-D ≥17	987 (26.9)	115 (24.8)	0.563	0.450-0.705	<0.001
	Participants with episodic HD	Participants with chronic HD	OR	95% CI	P
HAM-A ≥13	889 (63.0)	968 (76.8)	1.944	1.640-2.303	<0.001
HAM-A ≥25	250 (17.7)	486 (38.5)	2.915	2.441-3.481	<0.001
HAM-D ≥7	1,000 (70.8)	1,006 (79.8)	1.625	1.359-1.944	<0.001
HAM-D ≥17	431 (30.5)	556 (44.1)	1.795	1.532-2.104	<0.001
	Participants with MO	Participants without MO	OR	95% CI	P
HAM-A ≥13	503 (86.3)	1,354 (64.8)	3.418	2.655-4.399	<0.001
HAM-A ≥25	236 (40.5)	500 (23.9)	2.163	1.782-2.625	<0.001
HAM-D ≥7	515 (88.3)	2,491 (71.3)	3.043	2.322-3.986	<0.001
HAM-D ≥17	327 (56.1)	660 (31.6)	2.768	2.294-3.339	<0.001

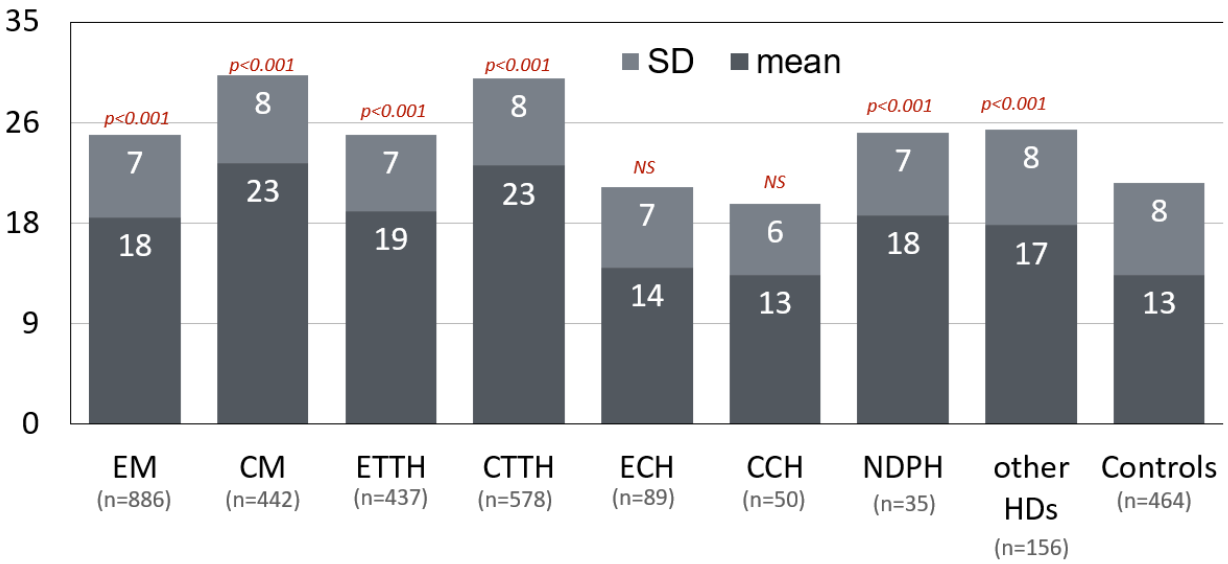

Figure 1: Mean±SD scores of Hamilton rating scales for anxiety by headache disorder.

SD, standard deviation; NS: non-significant; EM: Episodic Migraine; CM: Chronic Migraine; ETTH: Episodic Tension-Type Headache; CTTH: Chronic Tension-Type Headache; ECH: Episodic Cluster Headache; CCH: Chronic Cluster Headache; NDPH: New Daily Persistent Headache; HDs: Headache Disorders; Controls: non-headache participants.

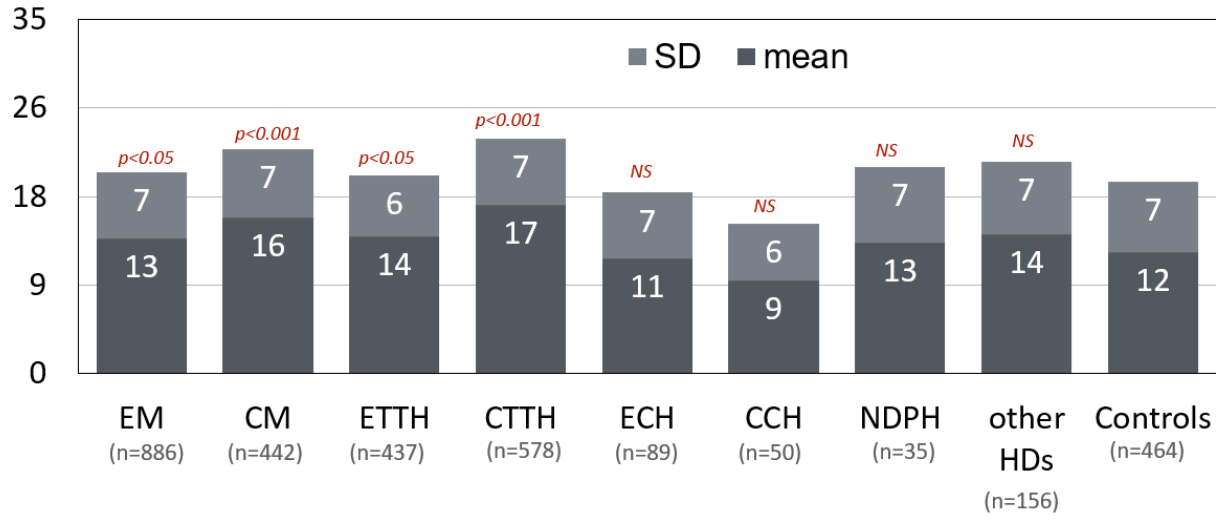

Figure 2: Mean±SD scores of Hamilton rating scales for depression by headache disorder.

SD, standard deviation; NS: non-significant; EM: Episodic Migraine; CM: Chronic Migraine; ETTH: Episodic Tension-Type Headache; CTTH: Chronic Tension-Type Headache; ECH: Episodic Cluster Headache; CCH: Chronic Cluster Headache; NDPH: New Daily Persistent Headache; HDs: Headache Disorders; Controls: non-headache participants.

Scores by headache type

The mean HAM-A and HAM-D scores for participants with migraine were 19.61±7.69 and 14.12±6.66 vs. 13.09±8.14 and 12.03±6.96 for non-headache participants. Participants with migraine had30% and 24.5% lower odds to score higher on the anxiety scale and depression scale respectively, compared to the TTH patients (OR=1.43, OR=1.32).HAM-A and HAM-D scores were higher in participants with migraine than those with cluster headache (OR=3.01 and 2.30, respectively). Individuals with chronic migraine scored higher in both scales than those with episodic migraine. The mean HAM-A and HAM-D scores for participants with TTH were 20.81±7.54 and 15.43±6.59. Participants with chronic TTH had higher scores for both scales **(Table 2 and 3, Figure 1 and 2).** The mean HAM-A and HAM-D scores for participants with cluster headache were 13.35± 6.69 and 10.61±6.31, respectively. Participants with MO had higher scores for both HAM-A and HAM-D scales vs. participants without MO (OR= 3.418, 95%CI: 2.655-4.399, p<0,001 for HAM-A, OR= 3.043, 95%CI: 2.322-3.986, p<0,001 for HAM-D). In addition, more participants with MO than participants without MO were scored ≥13 or ≥25 in HAM-A and≥ or ≥13 in HMA-D, indicating that more participants with MO were suffering from a mild or severe anxiety-like or depression-like condition than those without MO, respectively **(Table 4).**

Gender, education, and Age

Female participants had higher scores for both HAM-A and HAM-D in headache and non-headache participants and in all headache disorders, except for episodic cluster headache **(Figure 3).** The level of education was an important co-factor as well. Except for CH and NDPH, low education level was related with high scores in HAM-A and HAM-D in all HD **(Figure 3).** Age was not significantly contributed to the configuration of HAM-A and HAM-D scores, when analysed by headache types. For the case of MO, gender and education was significant co-factor. Females with MO had higher scores for both HAM-A and HAM-D than males, while high educated participants with MO also had higher scores for HAM-A and HAM-D than participants with MO and low education level. Age did not significantly affect the scoring in the context of MO.

Figure 3A

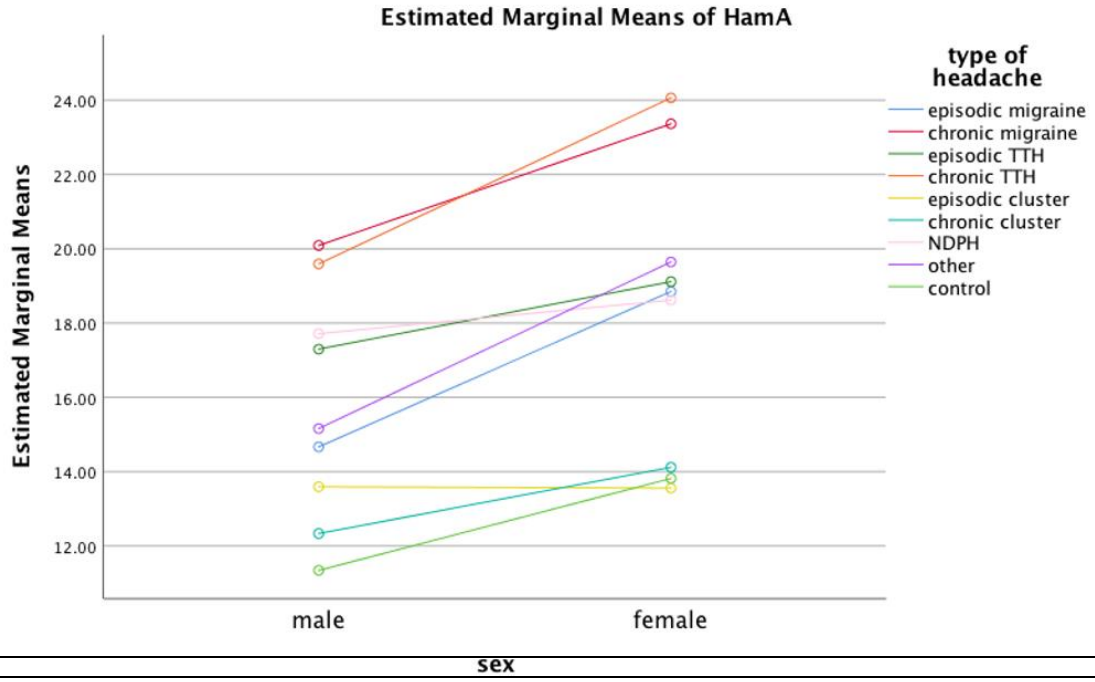

Figure 3B

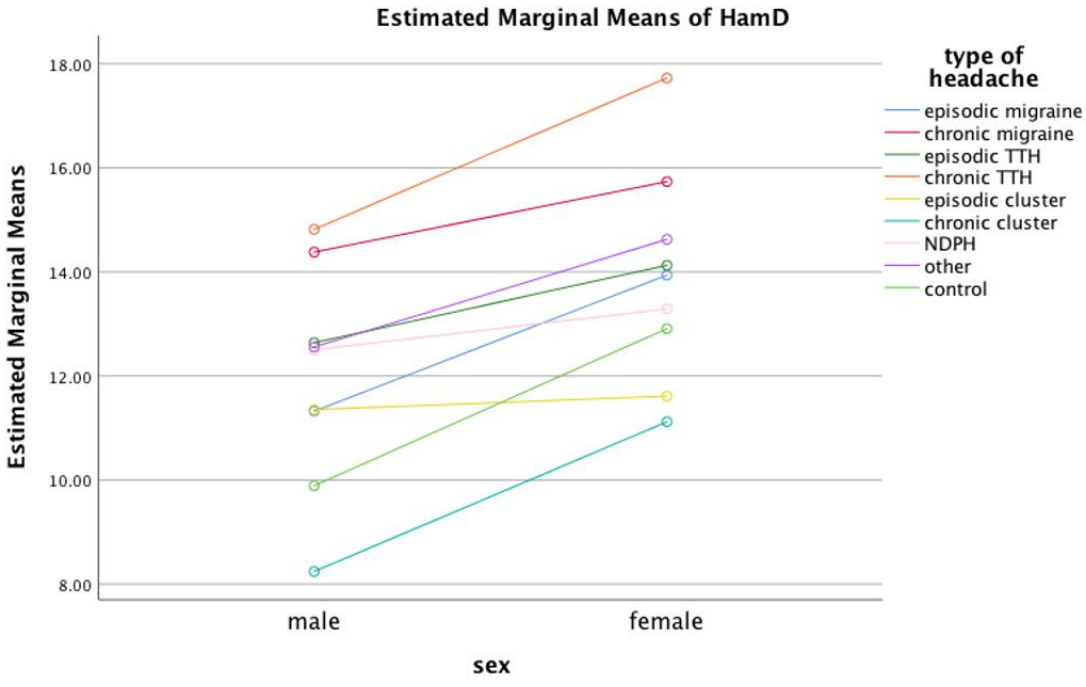

Figure 3C

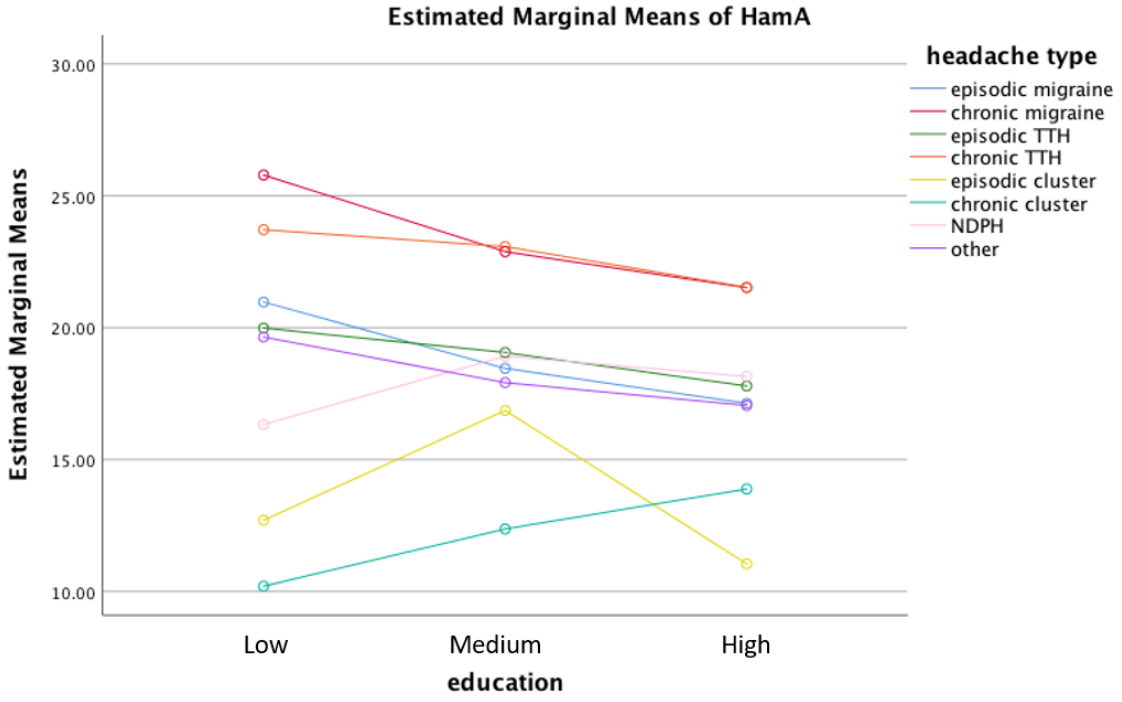

Figure 3D

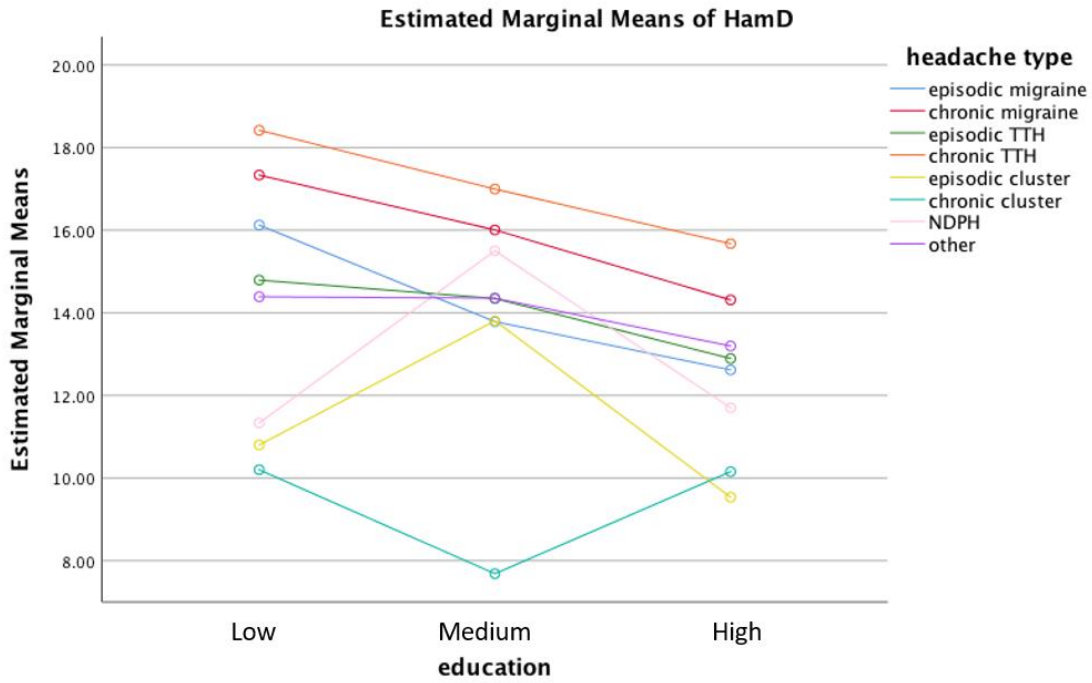

Figure 3: Estimated marginal means of Hamilton rating scales for Anxiety (A) and Depression (B) by headache disorder and gender or education.

Panels A and B: Female participants had higher scores for both HAM-A and HAM-D in headache and non-headache participants and in all headache disorders, except for episodic cluster headache. Panels C and D: Except for CH and NDPH, low education level was related with high scores in HAM-A and HAM-D in all HDs.

HamA: Hamilton rating scales for Anxiety; HamD: Hamilton rating scales for Depression; TTH: Tension-Type Headache; NDPH: New Daily Persistent Headache; HDs: Headache Disorders; Other: participants with other Headache Disorders; Control: non-headache participants.

Anxiety and depression symptoms

Sleep symptoms were very frequent among participants with HD and became more frequent among participants with chronic HD (OR=1.252, 95% CI: 1.075-1459, p=0004) and MO (OR=1.917, 95% CI: 1.592-2.309, p<0.001) vs. participants with episodic HD and no MO, respectively. The same pattern was observed for Gastrointestinal (GI) symptoms (OR=1.394, 95% CI: 1.193-1.629, p<0.001 and OR=1.510, 95% CI: 1.255-1817, p<0.001, respectively). Cardiovascular symptoms were very common as well, among participants with chronic vs. episodic HD (OR=1.394, 95% CI: 1.193-1.629, p=0.04), but MO did not affect reporting of cardiovascular symptoms (vs. participants without MO).

Discussion

In this cross-sectional survey, 27.5% of 2,673 individuals with headache who were attending the Aeginition out-patient headache clinic had severe anxiety symptoms, and 26.9% severe depressive symptoms (HAM-A and HAM-D score ≥25 and ≥17, respectively). Those with chronic HDs or MO showed much higher scores for both HAM-A (38.5% and 40.5%) and HAM-D (44.1% and 56.1%) than those with episodic HDs or no MO, respectively. In individuals with migraine HAM-A and HAM-D scores were higher than those with TTH or CH. Gender and education were important co-factors, but age was not. Female participants had higher scores for both HAM-A and HAM-D in headache and non-headache participants and in all types of HDs, except for episodic CH. Low education level was related with high scores in HAM-A and HAM-D in all HD, but not for CH and NDPH. Sleep, GI and cardiovascular symptoms were commonly reported, most often in chronic than in episodic HDs.

In a recent meta-analysis reporting information on 4.19 million people with primary HDs the most frequently addressed comorbidities were depressive disorders (23%; 95%CI: 20%–26%), hypertension (24%; 95%CI: 22%–26%), and anxiety disorders (25%; 95%CI: 22%–28%) **[11].** These estimates are close to those in the present study. Like in our study, females were more often comorbid with depression and anxiety disorders, but unlike in our study, young age was a significant risk factor for anxiety and depression **[11].** Education was not reported as a potential co variable. Why our study did not show that age is an important factor in the comorbidity of primary HDs with affective disorders, although the sample count was large, is not clear. It seems that other factors overshadow this relationship, possibly genetic, environmental, or even cultural. It is also highly likely that there is no such association between age and comorbidities of migraine with depression and anxiety.[12-14]Indeed, the authors of the

meta-analysis also admitted that their finding does not reflect a real relationship between age and comorbidity, but differences observed on the average age of subjects enrolled in the studies, above or below the age of 40.4 **[11].** Both our study in the meta-analysis agree that gender and education are significant co-factors in the comorbidity of anxiety and/or depression like symptoms with HDs, but the mechanism behind is not obvious either, generating several hypothetical etiopathogenetic thoughts. A common hypothesis supported by most, wants an interdependent relationship. However, even in this model it is not possible to determine the cause and effect, i.e., whether anxiety or depression caused the headache or vice versa. It seems more likely that the coexistence of the two conditions aggravates both, requiring much greater therapeutic effort on the part of the physician **[12-14].** Twin and family studies indicate that this bidirectional relationship can be explained, at least partly, by shared underlying genetically determined disease mechanisms. Although no genes have been robustly associated with the aetiology of both migraine and depression, genes from serotonergic, dopaminergic and GABAergic systems together with variants in the MTHFR and BDNF genes remain strong candidates **[13].**The choice of drugs for the treatment of both conditions is of particular interest, in addition. There are specific medicinal agents that may prevent from both condition and should be taken into consideration as first treatment option, in these cases **[14].** Non-pharmacological therapeutic approaches should also be deployed, e.g., cognitive behavioral treatment, physical therapy and/or neurostimulation **[15,16].**

As previously has been shown **[3],** the coexistence of depressive and anxiety like symptoms in people with HD and MO is higher compared to those without drug overuse. Individuals with MO showed a subtle psychopathological pattern characterized by impaired social adaptation **[17],** and depression, anxiety and stress **[18]** in other recent surveys confirming the findings of our study. Therefore, a person with a HD who overuses symptomatic drugs for headaches should be thoroughly checked for possible coexistence of anxiety or affective disorder. Such a person, who, in addition to very frequent headaches, also has symptoms of anxiety or depression, has a greater deterioration in his daily quality of life and needs special care. There are several methodological limitations that should be acknowledged. The survey was cross-sectional; therefore, it carries several disadvantages e.g., it cannot be used to analyze behavior over a period to time and it does not help determine cause and effect. In addition, the timing of the snapshot is not guaranteed to be representative. Data from individuals with MO Headache (MOH) are not reported, only from individuals with MO, because the later consist of individuals who although overuse medications, their headache frequency is not fluffing the “chronic criterion” (more than 15 days per month for more than three consecutive months). These individuals are at high risk for headache chronification and for MOH. On the other hand, the study design used in this survey offers the opportunity to compare many different variables at the same time, e.g., gender, age, headache type in relation to coexistence of depression and/or anxiety like symptoms with HD. Another advantage of this study is the relatively large sample of participants, given the fact that all they were underwent a phase-to-phase interview along with full neurological and physical examination to establish the diagnosis of headache.

Conclusion

In conclusion this survey shows that anxiety and depression-like symptoms are vary prevalent among individuals with HD, the chronic sub forms, or those with MO, in particular. It is speculated that these symptoms might trigger headache attacks acting as potential amplifiers of HD. Therefore, treating physicians are encouraged to screen people with headaches for possible anxiety and mood symptoms and, when such symptoms are detected, to manage them appropriately to prevent from headache recurrence or chronification.

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