

Regular Article

Generalized anxiety disorder, subthreshold anxiety and anxiety symptoms in primary headache

Giancarlo Lucchetti, MD,^{1*} Mario F. P. Peres, MD, PhD, FACP,^{1,2}

Alessandra L. G. Lucchetti, MD,³ Juliane P. P. Mercante, PhD,² Vera Z. Guendler, MSc² and Elioia Zukerman, PhD²

¹Department of Neurology, Federal University of São Paulo, ²Research Department, Albert Einstein Hospital, and ³Getúlio Vargas Foundation, São Paulo, Brazil

Aims: The aim of the present study was to evaluate the association between generalized anxiety disorder, subthreshold anxiety (SubAnx) and anxiety symptoms in the prevalence of primary headache.

Methods: This cross-sectional study evaluated 383 people from a Brazilian low-income community. One-year prevalence rates of migraine, chronic migraine and tension-type headache were calculated. Anxiety symptoms were then separated into the following groups (based on DSM-IV criteria): no anxiety criteria; one anxiety criterion; two anxiety criteria; and generalized anxiety disorder (GAD). The control group (no headaches) was compared with headache sufferers for each anxiety group using an adjusted model controlled for confounding factors.

Results: GAD was present in 37.0% of participants and SubAnx in 16.6%. Those with SubAnx had a 2.28-fold increased chance of having migraine;

3.83-fold increased chance of having chronic migraine, a 5.94-fold increased chance of having tension-type headache and a 3.27-fold increased chance of having overall headache. Some anxiety criteria (irritability, difficulty with sleep, concentration problems, muscle tension and fatigue) had similar prevalence to International Classification of Headache Disorders (ICHD-II) headache criteria such as unilateral pain and nausea for migraine and chronic migraine.

Conclusion: Headache sufferers seem to have a high prevalence of anxiety symptoms and SubAnx. In addition, the presence of two or more anxiety criteria (not necessarily fulfilling all the criteria for GAD) was associated with having a headache disorder.

Key words: anxiety, headache, migraine, subthreshold anxiety.

SEVERAL STUDIES HAVE associated migraine and primary headache with psychiatric disorders such as depression, bipolar disorder, social phobia, panic attack and personality traits.¹ Nevertheless, anxiety seems to have the strongest connection of them all.

Generalized anxiety disorder (GAD) is defined by a chronic and difficult-to-control worry/anxiety, which

includes somatic and psychiatric symptoms such as muscle tension, sleep disturbance, and fatigue.² Individuals with GAD have poorer quality of life, impairment in role functioning and other common medical problems, such as pain.^{2,3} Some studies show that 67% of GAD patients have migraine.⁴ Likewise, the prevalence of GAD in migraineurs is very high, ranging from 18% to 67%.^{5,6}

Other anxiety disorders such as panic disorder has also been linked to different types of headache such as tension-type headache (TTH) and new daily persistent headache.^{7,8}

Interestingly, there is a reciprocal relationship between GAD and migraines. Those with GAD have a

*Correspondence: Giancarlo Lucchetti, MD, Department of Neurology, Federal University of São Paulo, Rua Dona Elisa, 150 apto 153B, Barra Funda, São Paulo, CEP 01155030, Brazil.
Email: g.lucchetti@yahoo.com.br
Received 9 March 2012; revised 28 June 2012; accepted 27 July 2012.

threefold chance of having migraine and those with migraine have a fourfold chance of GAD.⁹ This association could have implications for migraine treatment costs.¹⁰

Subthreshold anxiety (SubAnx) has recently gained the attention of psychiatrists. Subthreshold disorders are defined as those syndromes that, for some reason, do not fulfill all the criteria of threshold definitions.¹¹

Some epidemiological studies have noted a high prevalence of subthreshold psychiatric symptoms in the general population, which can affect the response to treatment, chronicity and disability.^{12–14}

All these anxiety symptoms could have important repercussions for the neurologist. If there is a connection between SubAnx and headache, it could have clinical implications for those treating these disorders. A discussion regarding an early treatment for anxiety symptoms (even without GAD) to prevent primary headache could foster new prospective studies in this area, and may lead to earlier interventions in the future.

Within this context, we selected a non-clinical group (general population) from a low-income community (shantytown), in which the residents live under extreme conditions such as poverty, lack of sanitation and criminality.

These conditions are likely responsible for higher levels of psychiatric and physical disorders. In other words, the extreme cases throw light on the non-extreme.¹⁵

The aim of the present study was therefore to evaluate if there is an association between GAD, SubAnx and anxiety symptoms in primary headache prevalence.

METHODS

Local and type of study

This was an observational, cross-sectional study. We conducted door-to-door interviews of 439 subjects aged ≥ 18 year, from a Brazilian low-income community named *Paraisópolis*, located in the city of São Paulo, Brazil.

This informal settlement has approximately 60 000 inhabitants and 11 223 houses, which occupy 85 ha in the Morumbi district (South-west São Paulo, Brazil). According to a recent publication, at least 52.4% of households have an income < 3 Brazilian

minimum wage (BMW) and 24% have an income < 1 BMW.¹⁶ The name *Paraisópolis* means 'Paradise City' in Portuguese.

Procedures

The full study methodology has been described in previous articles^{17–19} and thus, is only summarized here. We randomly selected households according to the sectors included in the Albert Einstein Family Health Program number 2 (AEFHP2). This program, which operates in the Paraisópolis community, consists of visits to families in order to collect information, institute preventive action, and direct those in need to the Basic Healthcare Units.

AEFHP2 has 34 Family Health agents and approximately 3400 households included (100 per agent). Ten agents and 45 households for each agent were randomly selected, giving an expected total of 450 households (for a response rate of approximately 60%, i.e. 270 participants, with the exclusion of the non-eligible). Eleven households were not evaluated by the agents, leaving 439 for final analysis.

The interview was conducted by trained agents from the Family Health Program who presented the study objectives to the household resident and, if eligible, they were invited to participate. Only the person who answered the door was invited to participate. If this person was not eligible we asked for another eligible person in the household (only one person per household). We chose one person per household for the following reasons: (i) in this kind of personal-interview survey, if others are present during the interview, those who have already heard all the questions may give different answers from the initial respondent; (ii) the initial respondent may be compelled to answer personal questions; and (iii) more households can be evaluated by this method.

After the agreement, the volunteer signed written informed consent. An eligible respondent was aged > 18 years, was a permanent resident of the household, and was mentally capable of answering the questions.

The questionnaire was read to the participant by the interviewer. This headache questionnaire was based on one previously used in other study.²⁰ A test–retest reliability validation was done in 15% of the interviews, diagnosis was also doublechecked, when the patients came for an office visit, by a neurologist trained in headache disorders.¹⁸

Instruments

The questionnaire included the following.

1. Sociodemographic aspects.
2. Primary headache. This was based on the second edition of the International Classification of Headache Disorders (ICHD-II). Subjects were told to answer the questions based on their most frequent type of headache, if they had more than one type. Therefore, we gave only one diagnosis for each participant.
3. Migraine. This was diagnosed when all ICHD-II criteria were fulfilled and probable migraine diagnosis was made when all criteria were fulfilled but one.
4. TTH. This was diagnosed when all ICHD-II criteria were fulfilled (infrequent episodic TTH [IETTH]: at least 10 episodes occurring on <1 day per month on average [<12 days per year]; frequent episodic TTH [FETTH] at least 10 episodes occurring on ≥ 1 but <15 days per month for at least 3 months [≥ 12 and <180 days per year]). Probable TTH was diagnosed when all criteria were fulfilled but one.
5. Chronic migraine. This was diagnosed when respondents who fulfilled all ICHD-II criteria reported ≥ 15 days of headache per month.
6. Anxiety. This was evaluated using the Mini International Neuropsychiatric Interview (MINI)–Portuguese version validated by Amorim (kappa of 0.62, sensitivity of 0.67, specificity of 0.92, negative predictive value of 0.97 and positive predictive value of 0.79).²¹ Based on this instrument, we selected the following DSM-IV criteria: A, at least 6 months of 'excessive anxiety and worry' about a variety of events and situations; B, there is significant difficulty in controlling the anxiety and worry; c, the presence for most days over the previous 6 months of three or more of the following symptoms: feeling wound-up, tense, or restless; easily becoming fatigued or worn-out; concentration problems, irritability, significant tension in muscles and difficulty with sleep; D, the symptoms cause 'clinically significant distress' or problems functioning in daily life; E, not attributed to a medical condition, substance or its withdrawal or a psychiatry disorder.
7. Depression. This was evaluated using the MINI-Portuguese version validated by Amorim (kappa

of 0.68, sensitivity of 0.86, specificity of 0.84, negative predictive value of 0.92 and positive predictive value of 0.75).²¹ Based on this instrument, we made the diagnosis of major depressive disorder following the DSM-IV criteria.

Statistical analysis

One-year prevalence rates of migraine, chronic migraine and TTH were calculated in a previous study.¹⁸ We then used anxiety criteria A, B and C to subdivide the subjects into the following groups: no anxiety (control group), not fulfilling any anxiety criteria; one anxiety criterion, only one criterion (A, B or C) fulfilled in association with criteria D and E; two anxiety criteria, two criteria fulfilled (A and B, or A and C) in association with criteria D and E; GAD, all criteria fulfilled (A, B and C) in association with criteria D and E.

For the present study, we defined SubAnx as at least two anxiety criteria fulfilled in association with criteria D and E.

We analyzed the prevalence of overall headache, migraine, chronic migraine, tension-type migraine and no headache in each anxiety group (Fig. 1).

A multiple logistic regression (Enter method) was then conducted using presence of primary headache as the categorical dependent variable and anxiety groups as the independent variables, controlling for potential confounders. In this analysis, we analyzed

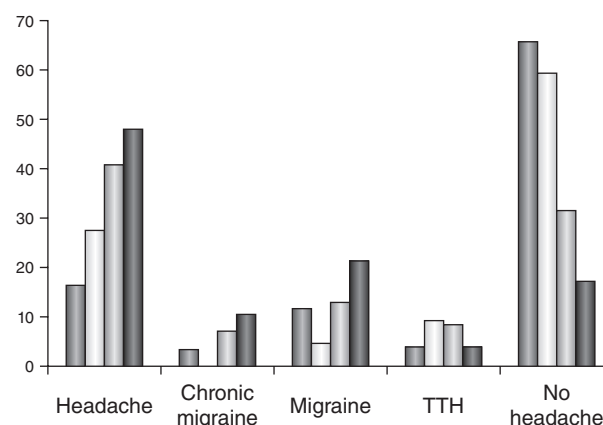


Figure 1. Percentage of patients with generalized anxiety disorder (GAD)/anxiety criteria and migraine, chronic migraine, episodic migraine, tension-type headache (TTH) and no headache. (□) No anxiety criteria; (▒) one anxiety criterion; (▓) two anxiety criteria; (■) GAD.

the odds of having several different primary headaches in each anxiety group.

For this procedure, we dichotomized primary headache as follows: presence of headache, 1 (yes) and 0 (no); presence of migraine, 1 (yes) and 0 (no); presence of chronic migraine, 1 (yes) and 0 (no); and presence of TTH, 1 (yes) and 0 (no).

We also created two distinct models for a better comprehension of the magnitude of the results: model 1, unadjusted model for anxiety groups; and model 2, adjusted model with confounding factors. For this analysis we used the following confounding factors: presence of depression (yes = 1, no = 0), gender (female = 1, male = 0) and job status (employed = 1, unemployed/retired = 0). Depression was selected because it is a very important confounding factor when studying the link between anxiety and migraine.²² Gender and employment status were selected because in a previous analysis of this sample they reached significance in the prevalence of primary headaches.¹⁸

The explained variance of each of the logistic regression models was calculated by means of the Nagelkerke R^2 , and the goodness of fit by means of the Hosmer and Lemeshow goodness-of-fit test.

Table 1 lists the comparisons between headache criteria and anxiety criteria for each type of headache. For this analysis, we used Fisher's exact test to compare one criterion with each other. The criteria with similar prevalence did not reach statistical significance ($P > 0.05$).

All data were double-entered and cross-checked for consistency. Data were analyzed using SPSS version 17 (SPSS, Chicago, IL, USA). $P \leq 0.05$ was considered statistically significant and odds ratio (OR) was presented with 95% confidence intervals (95%CI).

This study was approved by the Ethics Committee on Research of the Hospital Israelita Albert Einstein in São Paulo, Brazil.

RESULTS

A total of 439 households were contacted, but the questionnaire was filled out in 383 households (87.2%). In 56 the survey was not completed; some were excluded because respondents were not eligible, others because they did not complete the interview or they did not agree to participate.

In this setting there was a predominance of women (74.4%) between 18 and 39 years old. The mean age was 41.7 ± 8.5 years. Almost half of the subjects

reported a house income of <2 BMW, 51.2% were mixed race and approximately 30% were unemployed. Treated water supply was reported by 72.6%. A deeper socioeconomic analysis of this sample has been published elsewhere.¹⁸

Headache within the last year was reported by 172 subjects. The prevalence of migraine was 20.4%, chronic migraine 8.9%, TTH 6.2% and no headache 51.7%.

GAD was present in 37.0% of residents; two anxiety criteria/SubAnx (A and B, B and C, or A and C) were present in 16.6%; one anxiety criterion in 5.1%; and no anxiety criteria in 41.3%. Depression was present in 27.4%.

Figure 1 shows the prevalence of overall headache, migraine, chronic migraine, tension-type migraine and no headache in each anxiety group. We found a higher prevalence of primary headache in those persons with SubAnx and GAD.

Table 1 compares the prevalence of some headache diagnostic criteria and anxiety symptoms. After statistical analysis we found that some anxiety criteria had the same prevalence of some ICHD-II headache criteria as follows.

1. Chronic migraine: there was no statistical significance (indicating similar prevalence) between the following criteria: (I) 'unilateral pain' and fatigue ($P = 0.99$), muscle tension ($P = 0.14$); (II) 'pulsate pain' and fatigue ($P = 0.08$), irritability ($P = 0.14$), difficulty with sleep ($P = 0.08$); (III) 'moderate/severe pain intensity' and tension ($P = 0.77$), concentration problems ($P = 0.99$), irritability ($P = 1.00$), muscle tension ($P = 0.41$), difficulty with sleep ($P = 0.99$); (IV) 'aggravation by physical activity' and tension ($P = 0.36$), concentration problems ($P = 0.53$), irritability ($P = 0.75$), muscle tension ($P = 0.15$), difficulty with sleep ($P = 0.53$); (V) 'nausea' and tension ($P = 0.43$), fatigue ($P = 0.22$), concentration problems ($P = 0.29$), irritability ($P = 0.18$), muscle tension ($P = 0.80$), difficulty with sleep ($P = 0.29$); (VI) 'photo/phonophobia' and irritability ($P = 0.05$).
2. Migraine: there was no statistical significance (indicating similar prevalence) between the following criteria: (I) 'unilateral pain' and tension ($P = 0.06$), fatigue ($P = 0.99$), concentration problems ($P = 0.06$), muscle tension ($P = 0.32$), difficulty with sleep ($P = 1.00$); (II) 'nausea' and tension ($P = 0.85$), concentration problems ($P = 0.85$), irritability ($P = 0.85$), muscle tension ($P = 0.29$).

Table 1. Prevalence of headache diagnostic criteria and anxiety symptoms

Headache symptoms	Anxiety symptoms	Chronic Migraine	<i>P</i> [†]	Migraine	<i>P</i> [†]	TTH	<i>P</i> [†]
Unilateral location	Tense	47.0% × 73.5%	0.04	56.4% × 72.3%	0.06	20.8% × 65.2%	<0.01
	Fatigued	47.0% × 44.1%	0.99	56.4% × 58.0%	0.99	20.8% × 60.9%	<0.01
	Concentration	47.0% × 76.5%	0.02	56.4% × 72.3%	0.06	20.8% × 60.9%	<0.01
	Irritability	47.0% × 79.4%	0.01	56.4% × 72.3%	0.06	20.8% × 60.9%	<0.01
	Muscle tension	47.0% × 67.6%	0.14	56.4% × 64.9%	0.32	20.8% × 45.8%	0.12
	Sleep problems	47.0% × 75.8%	0.02	56.4% × 56.4%	1.00	20.8% × 52.2%	0.03
	GAD	47.0% × 36.7%	0.46	56.4% × 54.2%	0.87	20.8% × 17.4%	0.99
Pulsate pain	Tense	94.1% × 73.5%	0.04	89.7% × 72.3%	<0.01	20.8% × 65.2%	<0.01
	Fatigued	94.1% × 44.1%	<0.01	89.7% × 58.0%	<0.01	20.8% × 60.9%	<0.01
	Concentration	94.1% × 76.5%	0.08	89.7% × 72.3%	<0.01	20.8% × 60.9%	<0.01
	Irritability	94.1% × 79.4%	0.14	89.7% × 72.3%	<0.01	20.8% × 60.9%	<0.01
	Muscle tension	94.1% × 67.6%	0.01	89.7% × 64.9%	<0.01	20.8% × 45.8%	0.12
	Sleep problems	94.1% × 75.8%	0.08	89.7% × 56.4%	<0.01	20.8% × 52.2%	0.03
	GAD	94.1% × 36.7%	<0.01	89.7% × 54.2%	<0.01	20.8% × 17.4%	0.99
Moderate/severe pain intensity	Tense	79.4% × 73.5%	0.77	94.9% × 72.3%	<0.01	25.0% × 65.2%	0.01
	Fatigued	79.4% × 44.1%	<0.01	94.9% × 58.0%	<0.01	25.0% × 60.9%	0.01
	Concentration	79.4% × 76.5%	0.99	94.9% × 72.3%	<0.01	25.0% × 60.9%	0.01
	Irritability	79.4% × 79.4%	1.00	94.9% × 72.3%	<0.01	25.0% × 60.9%	0.01
	Muscle tension	79.4% × 67.6%	0.41	94.9% × 64.9%	<0.01	25.0% × 45.8%	0.22
	Sleep problems	79.4% × 75.8%	0.99	94.9% × 56.4%	<0.01	25.0% × 52.2%	0.07
	GAD	79.4% × 36.7%	<0.01	94.9% × 54.2%	<0.01	25.0% × 17.4%	0.72
Aggravation by physical activity	Tense	85.3% × 73.5%	0.36	87.2% × 72.3%	0.02	8.3% × 65.2%	<0.01
	Fatigued	85.3% × 44.1%	<0.01	87.2% × 58.0%	<0.01	8.3% × 60.9%	<0.01
	Concentration	85.3% × 76.5%	0.53	87.2% × 72.3%	0.02	8.3% × 60.9%	<0.01
	Irritability	85.3% × 79.4%	0.75	87.2% × 72.3%	0.02	8.3% × 60.9%	<0.01
	Muscle tension	85.3% × 67.6%	0.15	87.2% × 64.9%	<0.01	8.3% × 45.8%	0.07
	Sleep problems	85.3% × 75.8%	0.53	87.2% × 56.4%	<0.01	8.3% × 52.2%	<0.01
	GAD	85.3% × 36.7%	<0.01	87.2% × 54.2%	<0.01	8.3% × 17.4%	0.66
Nausea and/or vomiting	Tense	61.8% × 73.5%	0.43	74.4% × 72.3%	0.85	4.2% × 65.2%	<0.01
	Fatigued	61.8% × 44.1%	0.22	74.4% × 58.0%	0.04	4.2% × 60.9%	<0.01
	Concentration	61.8% × 76.5%	0.29	74.4% × 72.3%	0.85	4.2% × 60.9%	<0.01
	Irritability	61.8% × 79.4%	0.18	74.4% × 72.3%	0.85	4.2% × 60.9%	<0.01
	Muscle tension	61.8% × 67.6%	0.80	74.4% × 64.9%	0.29	4.2% × 45.8%	<0.01
	Sleep problems	61.8% × 75.8%	0.29	74.4% × 56.4%	0.02	4.2% × 52.2%	<0.01
	GAD	61.8% × 36.7%	0.05	74.4% × 54.2%	0.01	4.2% × 17.4%	0.34
Photo/phonophobia	Tense	97.1% × 73.5%	0.01	94.9% × 72.3%	<0.01	45.8% × 65.2%	0.38
	Fatigued	97.1% × 44.1%	<0.01	94.9% × 58.0%	<0.01	45.8% × 60.9%	0.38
	Concentration	97.1% × 76.5%	0.02	94.9% × 72.3%	<0.01	45.8% × 60.9%	0.38
	Irritability	97.1% × 79.4%	0.05	94.9% × 72.3%	<0.01	45.8% × 60.9%	0.38
	Muscle tension	97.1% × 67.6%	<0.01	94.9% × 64.9%	<0.01	45.8% × 45.8%	1.00
	Sleep problems	97.1% × 75.8%	0.02	94.9% × 56.4%	<0.01	45.8% × 52.2%	0.77
	GAD	97.1% × 36.7%	<0.01	94.9% × 54.2%	<0.01	45.8% × 17.4%	0.06

[†]Fisher's exact test ($P < 0.05$ statistically significant). Concentration, concentration problems; fatigued, easily fatigued or worn out; GAD, generalized anxiety disorder; muscle tension, significant tension in muscle; tense, feeling wound-up, tense or restless; TTH, tension-type headache.

Table 2. Logistic regression models for presence of primary headache[†]

	Headache (All) OR (95%CI)	Migraine OR (95%CI)	Chronic migraine OR (95%CI)	TTH OR (95%CI)
Unadjusted model (anxiety)				
No anxiety	1.00	1.00	1.00	1.00
One anxiety criterion	1.15 (0.41–3.22)	0.29 (0.03–2.34)	– [‡]	2.46 (0.45–13.35)
Two anxiety criteria	3.24 (1.75–5.97)***	2.69 (1.28–5.66)**	4.75 (1.35–16.72)***	4.62 (1.44–14.85)*
Generalized anxiety disorder	7.01 (4.18–11.75)***	7.82 (4.34–14.10)***	12.85 (4.54–36.31)***	3.89 (1.27–11.94)*
Unadjusted model (depression)				
No depression	1.00	1.00	1.00	1.00
Depression	2.47 (1.54–3.94)***	3.38 (2.01–5.67)***	3.83 (1.80–8.29)***	1.14 (0.40–3.26)
Adjusted model				
Anxiety				
No anxiety	1.00	1.00	1.00	1.00
One anxiety criterion	1.05 (0.36–3.00)	0.25 (0.03–2.05)	– [†]	2.01 (0.35–11.37)
Two anxiety criteria	3.27 (1.72–6.22)***	2.28 (1.04–5.01)*	3.83 (1.00–14.66)*	5.94 (1.69–20.90)**
GAD	6.63 (3.64–12.06)***	5.84 (2.94–11.59)***	13.18 (3.74–46.42)***	7.02 (1.92–25.67)**
Depression	1.03 (0.57–1.831)	1.32 (0.69–2.49)	1.54 (0.61–3.91)	0.63 (0.19–2.07)
Female gender	1.23 (0.71–2.13)	1.75 (0.84–3.61)	1.65 (0.40–6.71)	0.43 (0.15–1.21)
Employed person	2.48 (1.51–4.06)***	2.64 (1.50–4.67)***	5.72 (2.23–14.67)***	2.08 (0.77–5.58)
* <i>P</i> < 0.05; ** <i>P</i> < 0.01; *** <i>P</i> < 0.001. [†] GAD, subthreshold anxiety and anxiety symptoms given as risk factors. [‡] Not calculated due to sample size. CI, confidence interval; GAD, generalized anxiety disorder; OR, odds ratio; TTH, tension-type headache.				

3. TTH: there was no statistical significance (indicating similar prevalence) between the following criteria: (I) 'unilateral pain' and muscle tension (*P* = 0.12); (II) 'pulsate pain' and muscle tension (*P* = 0.12); (III) 'moderate/severe pain intensity' and muscle tension (*P* = 0.22), difficulty with sleep (*P* = 0.07); (IV) 'aggravation by physical activity' and, muscle tension (*P* = 0.07); (V) 'photo/phonophobia' and tension (*P* = 0.38), fatigue (*P* = 0.38), concentration problems (*P* = 0.38), irritability (*P* = 0.38), muscle tension (*P* = 1.00), difficulty with sleep (*P* = 0.77).

Table 2 lists the unadjusted and adjusted logistic regression models (enter method) for presence of different primary headache with GAD, SubAnx and anxiety symptoms as risk factors. In the adjusted model, we found the following. For presence of overall headache, two anxiety criteria (OR, 3.27; 95%CI: 1.72–6.22, *P* < 0.001) and GAD (OR, 6.63; 95%CI: 3.64–12.06, *P* < 0.001) were significant independent predictors. In this model, Nagelkerke *R*² was 0.255 and the Hosmer–Lemeshow goodness-of-

fit test was not significant ($\chi^2 = 11.968$, *P* = 0.153). For presence of migraine, two anxiety criteria (OR, 2.28; 95%CI: 1.04–5.01, *P* < 0.05) and GAD (OR, 5.84; 95%CI: 2.94–11.59, *P* < 0.001) were significant independent predictors. In this model, Nagelkerke *R*² was 0.305 and the Hosmer–Lemeshow goodness-of-fit test was not significant ($\chi^2 = 8.193$, *P* = 0.316). For presence of chronic migraine, two anxiety criteria (OR, 3.83; 95%CI: 1.00–14.66, *P* < 0.05) and GAD (OR, 13.18; 95%CI: 3.74–46.42, *P* < 0.001) were significant independent predictors. In this model, Nagelkerke *R*² was 0.362 and the Hosmer–Lemeshow goodness-of-fit test was not significant ($\chi^2 = 3.883$, *P* = 0.793). For presence of TTH, two anxiety criteria (OR, 5.94; 95%CI: 1.69–20.90, *P* < 0.01) and GAD (OR, 7.02; 95%CI: 1.92–25.67, *P* < 0.01) were significant independent predictors. In this model, Nagelkerke *R*² was 0.339 and the Hosmer–Lemeshow goodness-of-fit test was not significant ($\chi^2 = 3.616$, *P* = 0.823). Depression (significant in the unadjusted model) was weakened by anxiety in the adjusted model and did not reach statistical significance.

DISCUSSION

In the present study we found an association between SubAnx and primary headache, in which the presence of two or more anxiety criteria, not necessarily fulfilling all criteria for GAD, was associated with having a headache disorder.

This relationship, although not replicated in other settings as yet, sheds light on the possibility of early intervention for those patients with several anxiety symptoms not fulfilling all criteria for GAD.

Excessive worry and anticipatory anxiety are common in migraine patients. If we consider only the anxiety trait or feature, represented by some (not all) DSM-IV diagnostic criteria for GAD diagnosis, we will find anxiety a very common symptom of migraine.

We may even observe that some symptoms from the criterion C for anxiety based on DSM-IV ('feeling wound-up, tense or restless', 'concentration problems', 'irritability') are more common than unilateral pain location and similar to nausea, the clinical features that comprise the diagnostic criteria. For example, the prevalence of nausea in migraine was 74.4% in the present study, which is comparable to previous studies.²³ Some anxiety criteria such as irritability, difficulty with sleep, concentration problems, muscle tension and fatigue had similar prevalence compared with ICHD-II headache criteria such as unilateral pain and nausea for migraine.

One may speculate that anxiety symptoms are more related to the migraine syndrome symptomatology than the current symptoms present in the ICHD-II criteria. This could lead to a broader discussion on whether primary headache and, consequently other types of pain, could lead to anxiety or whether anxiety symptoms could foster primary headache. Nevertheless, the observation that headache patients suffer from high rates of various physical symptoms commonly seen in GAD (restlessness, fatigue, concentration problems, irritability, muscle tension, sleep problems) does not necessarily implicate GAD or even anxiety as the cause of these symptoms.

Indeed, there is an intrinsic relation between GAD and migraine in several studies.^{1,5,6} Some drugs available for migraine treatment can also have an impact on anxiety with good results, such as antidepressants, beta-blockers or benzodiazepines.²⁴ Recently, Gonda *et al.* found that the serotonin-transporter-linked polymorphic region (5HTTLPR) polymorphism of the serotonin transporter gene was

associated with anxiety disorders and also migraine, suggesting a common etiological background of these disorders.²⁵

The present study also found that those with TTH have lower prevalence of anxiety and anxiety symptoms than migraineurs. These results are in line with previous studies that found stronger associations between migraine and anxiety compared to non-migraine headaches.^{26–28} Other studies, however, have not found this association.⁵ Zwart *et al.* evaluated 51 383 individuals from a large cross-sectional population-based study in Norway and found that anxiety disorder as measured on the Hospital Anxiety and Depression Scale, was more associated with migrainous headache when compared with non-migrainous headache and headache-free individuals.²⁶

In clinical practice, there is a large number of headache sufferers who have mild anxiety symptoms, not fulfilling all DSM-IV GAD criteria. These patients usually have their anxiety symptoms disregarded and are not treated for this condition. Many current studies, however, have found that even those who do not fulfill all the criteria for a psychiatric disorder can also have comorbidity.^{12–14}

For example, some studies investigating subthreshold depression (SubD) found that SubD has an impact on conversion to major depression,^{29,30} increasing cognitive impairment,³¹ slowing recovery after hospitalization and increasing the suicidal ideation.²⁹

With regard to anxiety, fewer studies are available on SubAnx. SubAnx was associated with higher comorbidity and greater impairment,³² higher levels of psychological distress,³³ lower perceived health³³ and higher prevalence of other psychiatric disorders such as agoraphobia, panic disorder, alcohol use, depression and social phobia.³⁴

Recently, Blyth *et al.* evaluated the relation between worry about health, pain status and anxiety.³⁵ They found a strong correlation between 'sub-threshold anxiety-related factors' and pain. Beesdo *et al.* also found a relation between GAD and SubAnx with pain.³ They found those with SubAnx were two- to fourfold more likely to have pain than controls, whereas those with GAD were five- to 16-fold more likely, corroborating the present findings in migraine.

Some studies are also investigating the role of GAD treatment to reduce the onset of pain conditions and whether early intervention among individuals with pain decreases the risk for the development of

GAD, showing promising results.^{36,37} It is unknown whether these approaches will be effective in migraineurs.

The present results need to be interpreted with caution. First, it is a cross-sectional study, not allowing cause–effect conclusions. Second, Paraisópolis shantytown may not represent general communities worldwide, or all low-income communities, due to some local peculiarities, such as race and habitation status. In addition, in the present study a female majority was found, which can be explained by the following: (i) interviews were conducted during the day and some men were working at this time; (ii) usually in this type of community, women are responsible for housework; and (iii) women usually take care of their children at home and therefore, were eligible for the interview. Therefore, more studies are necessary in order to replicate these findings in other settings.

Third, the present sample was probably one of those responsible for the higher prevalence of anxiety symptoms due to extreme living conditions. This type of population suffers several types of stress such as, psychological, economical and social. These factors could have an influence on the connection between anxiety-headache and vice versa. The high prevalence of migraine and chronic migraine in the present study might be due to this.

Fourth, we used an arbitrary definition of SubAnx, because there is no formal consensus at this time; and fifth, although depression was not a significant predictor in the adjusted model, the depression variable was categorical (0 or 1). Future studies are needed to replicate these findings using continuous variables, with the Beck Depression Inventory and the State Trait Anxiety Inventory as measures of depression and anxiety, respectively.

In conclusion, headache sufferers seem to have a high prevalence of anxiety symptoms and SubAnx. Likewise, the presence of two or more anxiety criteria, not necessarily fulfilling all criteria for GAD, was associated with having a headache disorder. Neurologists should be aware of this relationship and evaluate their patients in this way. New studies are needed to replicate these findings and to investigate this association in clinical trials.

ACKNOWLEDGMENTS

The authors report no conflict of interest. No author or related institution has received any financial

benefit from research in this study except Giancarlo Lucchetti, who received a PhD scholarship from The National Council for Scientific and Technological Development, Brazil (CNPQ).

REFERENCES

1. Wang SJ, Chen PK, Fuh JL. Comorbidities of migraine. *Front. Neurol.* 2010; **1**: 16.
2. Lenze EJ, Rollman BL, Shear MK *et al.* Escitalopram for older adults with generalized anxiety disorder. *JAMA* 2009; **301**: 295–303.
3. Beesdo K, Hoyer J, Jacobi F, Low NCP, Höfler M, Wittchen HU. Association between generalized anxiety levels and pain in a community sample: Evidence for diagnostic specificity. *J. Anxiety Disord.* 2009; **23**: 684–693.
4. Senaratne R, Van Ameringen M, Mancini C, Patterson B, Bennett M. The prevalence of migraine headaches in an anxiety disorders clinic sample. *CNS Neurosci. Ther.* 2010; **16**: 76–82.
5. Beghi E, Bussone G, D'Amico D *et al.* Headache, anxiety and depressive disorders: The HADAS study. *J. Headache Pain* 2010; **11**: 141–150.
6. Radat F, Mekies C, Geraud G *et al.* Anxiety, stress and coping behaviours in primary care migraine patients: Results of the SMILE study. *Cephalalgia* 2008; **28**: 1115–1125.
7. Peres JF, Gonçalves AL, Peres MF. Psychological trauma in chronic pain: Implications of PTSD for fibromyalgia and headache disorders. *Curr. Pain Headache Rep.* 2009; **13**: 350–357.
8. Peres MF, Lucchetti G, Mercante JP, Young WB. New daily persistent headache and panic disorder. *Cephalalgia* 2011; **31**: 250–253.
9. McWilliams LA, Goodwin RD, Cox BJ. Depression and anxiety associated with three pain conditions: Results from a nationally representative sample. *Pain* 2004; **111**: 77–83.
10. Pesa J, Lage MJ. The medical costs of migraine and comorbid anxiety and depression. *Headache* 2004; **44**: 562–570.
11. Helmchen H, Linden M. Subthreshold disorders in psychiatry: Clinical reality, methodological artifact, and the double-threshold problem. *Compr. Psychiatry* 2000; **41**: 1–7.
12. Saravay SM, Lavin M. Psychiatric comorbidity and length of stay in the general hospital. A critical review of outcome studies. *Psychosomatics* 1994; **35**: 233–252.
13. Olfson M, Broadhead WE, Weissman MM *et al.* Subthreshold psychiatric symptoms in a primary care group practice. *Arch. Gen. Psychiatry* 1996; **53**: 880–886.
14. Altamura AC, Montresor C, Salvadori D, Mundo E. Does comorbid subthreshold anxiety affect clinical presentation and treatment response in depression? A preliminary 12-month naturalistic study. *Int. J. Neuropsychopharmacol.* 2004; **7**: 481–487.

15. James W. The varieties of religious experience. *Am. Relig. Hist.* 1902; 1958: 244–253.
16. da Silva EN, Ribeiro H. [Temperature modifications in shantytown environments and thermal discomfort]. *Rev. Saude Publica* 2006; 40: 663–670.
17. Lucchetti G, Granero Lucchetti AL, Peres MF, Leao FC, Moreira-Almeida A, Koenig HG. Validation of the Duke Religion Index: DUREL (Portuguese Version). *J. Relig. Health* 2012; 51: 579–586.
18. Lucchetti G, Peres MF. The prevalence of migraine and probable migraine in a Brazilian favela: Results of a community survey. *Headache* 2011; 51: 971–979.
19. Lucchetti G, Peres MFP, Lucchetti ALG, Koenig HG. Religiosity and tobacco and alcohol use in a Brazilian shantytown. *Subst. Use Misuse* 2012; 47: 837–846.
20. Mercante JP, Peres MF, Guendler V, Zukerman E, Bernik MA. Depression in chronic migraine: Severity and clinical features. *Arq. Neuropsiquiatr.* 2005; 63: 217–220.
21. Amorim P. Mini International Neuropsychiatric Interview (MINI): Validation of a short structured diagnostic psychiatric interview. *Rev. Bras. Psiquiatr.* 2000; 22: 106–115.
22. Radat F, Swendsen J. Psychiatric comorbidity in migraine: A review. *Cephalalgia* 2005; 25: 165–178.
23. Lipton RB, Stewart WF, Diamond S, Diamond ML, Reed M. Prevalence and burden of migraine in the United States: Data from the American Migraine Study II. *Headache* 2001; 41: 646–657.
24. Finocchi C, Villani V, Casucci G. Therapeutic strategies in migraine patients with mood and anxiety disorders: Clinical evidence. *Neurol. Sci.* 2010; 31 (Suppl. 1): S95–S98.
25. Gonda X, Rihmer Z, Juhasz G, Zsombok T, Bagdy G. High anxiety and migraine are associated with the s allele of the 5HTTLPR gene polymorphism. *Psychiatry Res.* 2007; 149: 261–266.
26. Zwart JA, Dyb G, Hagen K *et al.* Depression and anxiety disorders associated with headache frequency. The Nord-Trøndelag Health Study. *Eur. J. Neurol.* 2003; 10: 147–152.
27. Mongini F, Ciccone G, Deregibus A, Ferrero L, Mongini T. Muscle tenderness in different headache types and its relation to anxiety and depression. *Pain* 2004; 112: 59–64.
28. Karwautz A, Wöber C, Lang T *et al.* Psychosocial factors in children and adolescents with migraine and tension-type headache: A controlled study and review of the literature. *Cephalalgia* 1999; 19: 32–43.
29. Meeks TW, Vahia IV, Lavretsky H, Kulkarni G, Jeste DV. A tune in 'a minor' can 'b major': A review of epidemiology, illness course, and public health implications of sub-threshold depression in older adults. *J. Affect. Disord.* 2011; 129: 126–142.
30. Wells KB, Burnam MA, Rogers W, Hays R, Camp P. The course of depression in adult outpatients. Results from the Medical Outcomes Study. *Arch. Gen. Psychiatry* 1992; 49: 788–794.
31. Han L, McCusker J, Cole M, Abrahamowicz M, Capek R. 12-month cognitive outcomes of major and minor depression in older medical patients. *Am. J. Geriatr. Psychiatry* 2008; 16: 742–751.
32. Fehm L, Beesdo K, Jacobi F, Fiedler A. Social anxiety disorder above and below the diagnostic threshold: Prevalence, comorbidity and impairment in the general population. *Soc. Psychiatry Psychiatr. Epidemiol.* 2008; 43: 257–265.
33. Rucci P, Gherardi S, Tansella M *et al.* Subthreshold psychiatric disorders in primary care: Prevalence and associated characteristics. *J. Affect. Disord.* 2003; 76: 171–181.
34. Carter RM, Wittchen HU, Pfister H, Kessler RC. One-year prevalence of subthreshold and threshold DSM-IV generalized anxiety disorder in a nationally representative sample. *Depress. Anxiety* 2001; 13: 78–88.
35. Blyth FM, Cumming RG, Nicholas MK *et al.* Intrusive pain and worry about health in older men: The CHAMP study. *Pain* 2011; 152: 447–452.
36. Moore JE, VonKorff M, Cherkin D, Saunders K, Lorig K. A randomized trial of a cognitive-behavioral program for enhancing back pain self care in a primary care setting. *Pain* 2000; 88: 145–153.
37. Von Korff M, Balderson BH, Saunders K *et al.* A trial of an activating intervention for chronic back pain in primary care and physical therapy settings. *Pain* 2005; 113: 323–330.