**STUDY INFORMATION**

Title: Anxiety, depression and headache-related disability in a large pediatric cohort

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Description:

The primary objective of this study is to examine the association between headache-related disability and self-report of anxiety and/or depression for a large clinic sample of adolescents.

Primary Hypothesis: Patients with a self-reported diagnosis of anxiety, depression, or both will report a higher headache-related disability compared to patients in this sample who do not report these diagnoses.

Secondary Hypotheses:

1. Self-reported involvement with a behavioral health provider will reduce the association between headache-related disability and having a diagnosis of anxiety, depression, or both

1. Patients with diagnoses of anxiety, depression, or both will report a higher number of headache associated-symptoms compared to patients who do not report these diagnoses.

Background:

The connection between anxiety, depression, and pediatric headache disorders has been well established (i.e., O’Brien & Slater, 2016; Senturk et al., 2018; Slater et al., 2012). In fact, a recent meta-analysis indicated a significant association between migraine and depressive symptoms as well as significantly higher odds of anxiety and depressive disorders in children and adolescents with migraine, compared to those without, with no differences found across clinic or population based samples (Fall et al., 2022). While the connection between anxiety, depression, and various headache types has been established, less is understood about whether patients with internalizing symptoms have unique headache characteristics such as pain location, quality, triggers etc.). Researchers are trying to understand why patients with headache and migraine are more likely to have internalizing disorders, with hypotheses related to underlying involvement from the HPA axis, hormonal changes, and serotonergic dysfunction (Ozge et al., 2018). In addition to having clinical implications for diagnosis and treatment, better understanding of the relationship between anxiety, depression, and specific headache characteristics may also shed light on the neurobiological connection between the biological and behavioral disorders.

Children with frequent or severe headaches are also more likely to experience functional impairment such as missed school days, missed activities, and poor adherence to responsibilities. In a recent study including over 57,000 children, results showed that headache became more strongly associated with missed school days over an eight-year span, indicating a growing need to address the dynamic needs of this population (Pawlowski et al., 2019). To date, very little is understood about the relationship between anxiety, depression, and headache burden, including functional impairment. It will be essential to understand the connection between anxiety, depression, and all aspects of headache burden in order to develop treatment plans that are considerate of the burden headache disorders may have on a patient’s entire ecological network.

The current study will utilize a large data registry of pediatric patients referred to a tertiary care site for headache management. The study aims to provide helpful insight into the prevalence of anxiety and depression for a clinic population, as well as novel understanding of the association between anxiety, depression, and specific headache characteristics as well as headache burden, including functional impairment. Results will have implications for clinical management of pediatric headache patients with the aim of reducing pain related disability and optimizing functional status.

**DESIGN PLAN**

This is a pre-registered single site cross-sectional study conducted from patient questionnaires collected at the Children’s Hospital of Philadelphia general neurology and headache outpatient clinics. The study aims to establish the prevalence of self-reported anxiety and depression as well as the relationship between these internalizing disorders and reports of headache-related disability. This study also will explore whether self-reported involvement with a behavioral health provider will moderate the relationship between having a diagnosis of anxiety and/or depression and headache-related disability.

Inclusion criteria: Youth must meet the following inclusion criteria. (1) ages 6 to 17 years old at the time the questionnaire was filled out (2) includes answers on the main predictor and main outcome; (3) any sex, any race/ethnicity; (4) filled out the CHOP intake headache questionnaire between June 2017 and January 2023; (5) any headache diagnosis

Exclusion criteria: (1) data outside of the designated age (2) outside the date collection range

Participant demographics including age, sex (or gender including the categories of cisgender male, cisgender female, transgender male, transgender female, non-binary if data are available), and race/ethnicity will be assessed, and the presence of ADHD, which was frequently reported (>10%) in the cohort. Other psychiatric diagnoses will not be included because they are reported in low frequency (<5%).

Participants will be grouped into the following categories :

1. Those who report no anxiety or depression
2. Those who report anxiety only
3. Those who report depression only
4. Those who report anxiety and depression

These categorizations will be based on patient response to select all that apply under the category of “behavioral health” when reporting on current and past medical history. Options include “none, attention deficit/hyperactivity disorder, anxiety/panic attacks, depression, behavior problems, oppositional defiance, obsessive compulsive disorder, autism spectrum disorder, social worker involved, psychologist involved, psychiatrist involved”.

Our primary outcome will be headache-related disability (PedMIDAS grade, none, mild, moderate, and severe). Grades will be used instead of raw score because raw scores are highly skewed.

We will consider headache burden metrics and associated headache features through multiple correspondence analysis (Patterson Gentile et al., submitted).

Headache burden metrics will include the following

1. Baseline pain severity (mild, moderate, severe scale)
2. Frequency of severe headache exacerbations
3. Pain pattern (constant vs. intermittent)
4. Impairment (p7 “how often do the headaches get in the way of what you want to do?”)

Additional headache characteristics will include the following

1. Associated symptoms (associated symptom count, and as secondary analysis will also look at MCA factor loadings dimension 1 and 2 from Patterson Gentile et al, under review)
2. Triggers (total trigger count, and individual triggers)
3. ICHD-3 Headache diagnosis as determined by a previously reported algorithm applied to patient data (Patterson Gentile et al, 2023)

**ANALYSIS PLAN**

All analyses will be carried out through Matlab®.

The goal of this study is to better characterize headache burden, associated symptoms, and headache features associated with anxiety and depression in children. We will perform univariate analysis comparing the four groups across patient demographics, and multiple headache characteristics as outlined above. Proportions will be reported for binary and categorical data, median and interquartile range for ordinal and non-normal continuous data and mean and standard error of the mean for normal interval data. Chi squared will be reported for binary and categorical data, Kruskal-Wallis will be reported for ordinal data and non-normal interval data, and ANOVA will be reported for normal interval data. Benjamini-Hochberg correction will be used to determine significance in the case of multiple comparisons (eg. associated symptoms, triggers). Given the large dataset, we will also report effect sizes for significant variables. Associated symptoms will be compared individually and with multiple correspondence analysis determined from prior work (Patterson Gentile et al, under review).

Based on previous research, the following covariates will be accounted for in all analyses: gender, age, current involvement with a behavioral health provider, current involvement with a psychiatrist.

We will perform logistic regression analysis to determine covariates that significantly correlate with the presence or absence of anxiety/depression. Our main predictor will be the presence of anxiety and/or depression, and our main outcome will be headache-related disability as measured by pedMIDAS grade (none, mild, moderate, severe). The following covariates will be included in analyses regardless of significance on univariate testing: age, sex/gender, race, ethnicity, and the interaction between self-reported involvement with a behavioral health provider and self-report of anxiety/depression. Additional covariates will be included if they are significantly associated with anxiety and/or depression, or any of the outcome variables (p>0.1, or p>0.1 corrected for Benjamini-Hochberg in the case of multiple comparisons like triggers): headache pattern (continuous vs. intermittent), frequency of moderate to severe headache days, overall headache severity (mild, moderate, severe), associated symptoms count.

We will also perform a sub-analysis of those reporting anxiety and/or depression and determine if self-reported involvement in a behavioral health professional impacts headache burden metrics.

For missing data, we will compare those excluded based on missing data to those who were included across demographics and headache characteristics. We will report missing data rates for all statistical comparisons and plan to employ propensity scoring if there is a large amount of missing data (>5%) and/or are substantial differences between those excluded based on missing data.

Sample size: Not applicable given large dataset

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