

The Associations Between Preexisting Mental Disorders and Subsequent Onset of Chronic Headaches: A Worldwide Epidemiologic Perspective

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Abstract: Although there is a significant association between preexisting depression and later onset of chronic headache, the extent to which other preexisting mental disorders are associated with subsequent onset of headache in the general population is not known. Also unknown is the extent to which these associations vary by gender or by life course. We report global data from the WHO's World Mental Health surveys ($n = 52,095$), in which, by means of the Composite International Diagnostic Interview–3.0, 16 mental disorders from the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*, were retrospectively assessed in terms of lifetime prevalence and age of onset. Frequent or severe headaches were assessed using self-reports. After adjustment for covariates, survival models showed a moderate but consistent association between preexisting mood (odds ratios [ORs] = 1.3–1.4), anxiety (ORs = 1.2–1.7), and impulse-control disorders (ORs = 1.7–1.9) and the subsequent onset of headache. We also found a dose-response relationship between the number of preexisting mental disorders and subsequent headache onset (OR ranging from 1.9 for 1 preexisting mental disorder to 3.4 for ≥ 5 preexisting mental disorders). Our findings suggest a consistent and pervasive relationship between a wide range of preexisting mental disorders and the subsequent onset of headaches. This highlights the importance of assessing a broad range of mental disorders, not just depression, as specific risk factors for the subsequent onset of frequent or severe headaches.

Perspective: *This study shows that there is a temporal association between a broad range of preexisting mental disorders and the subsequent onset of severe or frequent headaches in general population samples across the world.*

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Key words: *Epidemiology, preexisting mental disorders, headache onset.*

Headaches are among the most common pain conditions around the world, with 12-month prevalence around 11 to 14%.^{24,38,47} Headaches are oftentimes associated with emotional problems and occur about twice as often in persons with depressive/anxiety disorders than in those without.^{45,48} Most studies assessed 12-month or lifetime comorbidity patterns between mental disorders and headaches, but studies investigating temporal relationships between mental disorders and headaches are much scarcer.^{2,7,9,10,17,25,28} Most evidence exists for depression as a specific risk factor for the onset of headaches and for the transformation of episodic into chronic headaches.^{3,12,50} Moreover, there has been longstanding interest in the relationship between anger (the main feature of intermittent explosive disorder [IED]) and chronic headache, but knowledge about this association is far from conclusive.³⁴ The extent to which other mental disorders are associated with the incidence of headache remains largely unclear. This leaves the uncertainty as to whether the relationship between emotional problems and pain is solely confined to depression or reflects a broader spectrum of mental disorders beyond depressive symptomatology.^{11,19,27} No global data exist that investigate the associations between a broad range of common mental disorders and the subsequent onset of headaches, as most studies were confined to a limited number of countries (the United States, Canada, Italy, China, and The Netherlands).^{8,15,17,18,25,46}

Further, among the limited number of studies that assessed the temporal association of more than 1 mental dis-

order with headache, many studies entirely focus on the effects of specific disorders, without controlling for the effects of the coexistence of multiple mental disorder comorbidities. This means that in prior studies, dose-response relationships have never been examined. Other related fundamental gaps in our understanding include to what extent the number of mental disorders is associated with increased odds of subsequent headaches or whether associations vary by gender or across the life course.

Here, we report general population surveys from the World Mental Health (WMH) surveys that retrospectively assessed a broad range of lifetime *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*, mental disorders and a broad range of self-reported chronic physical conditions. The present study builds on earlier WMH studies on the relationships between mental disorders and headaches. These found high comorbidity between mental disorders and headaches but also found that early-onset depression/anxiety disorders (ie, onset before the age of 21 years) were moderately but consistently (ie, odds ratios [ORs] between 1.61 and 1.76) related to headache onset after the age of 21 years.^{24,41,47} Here, we address each of the aforementioned limitations by conducting cross-national analyses of the timing between a broad range of preexisting mental disorders and the odds of subsequent onset of headaches. Our aims were 1) to investigate the association of preexisting mood, anxiety, impulse control, and substance use disorders with subsequent onset of frequent or severe headaches, with and without adjustment for mental disorder comorbidity; 2) to assess whether an increasing

number of preexisting mental disorders is associated with increasing odds of headache in a dose-response relationship; and 3) to analyze to what extent associations vary by gender or across the life course. This latter investigation has 2 components: we examined the effect of variation in the timing of the mental disorder predictor (ie, early- vs late-onset preexisting mental disorders) and also the effect of variation in the time in the respondent's life at which the headache onset occurred.

Methods

Setting and Participants

This study used data from 19 of the WMH surveys: Colombia, Mexico, Peru, United States, Shenzhen (China), Japan, New Zealand, Belgium, France, Germany, Italy, The Netherlands, Romania, Spain, Portugal, Israel, Iraq, Northern Ireland, and Poland (Table 1). A stratified multistage clustered area probability sampling strategy was used to select adult respondents (aged ≥ 18 years) in most WMH countries. Most of the surveys were based on nationally representative household samples, whereas those of Colombia, Mexico, and Shenzhen were based on nationally representative household samples in urbanized areas.

In most countries, internal subsampling was used to reduce respondent burden and average interview time by dividing the interview into 2 parts. All respondents

($N = 98,714$) completed Part 1, which included the core diagnostic assessment of most mental disorders. All Part 1 respondents who met lifetime criteria for any mental disorder and a probability sample of other respondents ($n = 52,095$) were administered Part 2, which assessed physical conditions and collected a range of other information related to survey aims. Part 2 respondents were weighted by the inverse of their probability of selection for Part 2 of the interview to adjust for differential sampling. The section on mental disorders as well as the section on physical conditions (including the question on frequent or severe headaches) were administered in the entire Part 2 sample, which contained persons with and also without mental disorders. Because WMH analyses systematically feature comparisons between persons with and those without mental disorders, and because the number of noncases exceeds the number of cases, the undersampling of persons without mental disorders in Part 2 had virtually no effect on statistical power to study correlates of disorder.

Analyses in this paper are based on the weighted Part 2 subsample. Additional weights were used to adjust for differential probabilities of selection within households, to adjust for nonresponse, and to match the samples to population sociodemographic distributions. Measures taken to ensure interviewer and data accuracy and cross-national consistency are described in detail elsewhere.²¹ All respondents provided informed consent, and procedures for protecting respondents were approved and

Table 1. Characteristics of WMH Samples and Percent (and Number) With History of Frequent or Severe Headaches

COUNTRY	FIELD DATES	AGE RANGE	SAMPLE SIZE			HISTORY OF HEADACHES		
			PART 1	PART 2 SUBSAMPLE	RESPONSE RATE (%)	NUMBER UNWEIGHTED (N)	WEIGHTED (%)	
Americas								
Colombia	2003	18–65	4,426	2,381	87.7	814	27.8	
Mexico	2001–2002	18–65	5,782	2,362	76.6	565	16.4	
United States	2002–2003	≥ 18	9,282	5,692	70.9	1660	22.7	
Peru	2005–2006	18–65	3,930	1,801	90.2	431	18.9	
Asia and South Pacific								
Japan	2002–2006	≥ 20	4,129	1,682	55.1	236	10.9	
PRC Shenzhen	2006–2007	≥ 18	7,132	2,475	80.0	257	6.7	
New Zealand	2003–2004	≥ 18	12,790	7,312	73.3	2100	22.7	
Europe								
Belgium	2001–2002	≥ 18	2,419	1,043	50.6	217	17.7	
France	2001–2002	≥ 18	2,894	1,436	45.9	421	24.5	
Germany	2002–2003	≥ 18	3,555	1,323	57.8	298	17.9	
Italy	2001–2002	≥ 18	4,712	1,779	71.3	394	17.2	
The Netherlands	2002–2003	≥ 18	2,372	1,094	56.4	257	16.5	
Spain	2001–2002	≥ 18	5,473	2,121	78.6	475	15.5	
Northern Ireland	2004–2007	≥ 18	4,340	1,986	68.4	345	16.9	
Portugal	2008–2009	≥ 18	3,849	2,060	57.3	704	26.6	
Romania	2005–2006	≥ 18	2,357	2,357	70.9	395	16.2	
Poland	2010–2011	18–64	10,081	4,000	50.4	672	12.7	
Middle East								
Israel	2002–2004	≥ 21	4,859	4,859	72.6	1140	23.6	
Iraq	2006–2007	≥ 18	4,332	4,332	95.2	990	20.8	
Weighted average response rate (%)						78.0		
Total sample size			98,714	52,095		12371		

monitored for compliance by the institutional review boards in each country.³³

Training and Field Procedures

The central WMH staff trained bilingual supervisors in each country. Consistent interviewer training documents and procedures were used across surveys. The WHO translation protocol was used to translate instruments and training materials. Translations were performed by bilingual translators in consultation with expert panels (consisting of psychiatrists, psychologists, and mental health researchers). The following steps were performed: translation from the original (English version into the target language by 2 independent translators), review of these translations by a group of bilingual people and production of a revised version, translation of the revised version back into English by 2 translators; and review of the back-translations and production of a final version by the group of bilingual persons. Cross-cultural validations of the original Composite International Diagnostic Interview (CIDI) instrument have been conducted in the past, yielding acceptable outcomes.⁵²

Interviews were carried out in the country's official languages or in the region's dominant languages. Standardized descriptions of the goals and procedures of the study, data uses and protection, and the rights of respondents were provided in both written and verbal form to all potentially eligible respondents before obtaining verbal informed consent for participation in the survey. Quality control protocols, described in more detail elsewhere, were standardized across countries to check on interviewer accuracy and to specify data cleaning and coding procedures.²¹

Measures

Mental Disorders

All surveys used the third version of the CIDI-3.0, a fully structured psychiatric interview, to assess lifetime history of mental disorders. Disorders were assessed using the definitions and criteria of the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*.²¹ The mental disorders included in this paper are anxiety disorders (panic disorder, agoraphobia without panic, specific phobia, social phobia, posttraumatic stress disorder, generalized anxiety disorder, obsessive compulsive disorder); mood disorders (major depressive disorder/dysthymia, bipolar disorders I, II, and broad); substance use disorders (alcohol abuse and dependence, drug abuse and dependence); and impulse control disorders (IED, bulimia nervosa, and binge eating disorder). CIDI organic exclusion rules were applied in making diagnoses. The clinical reappraisal studies carried out in 4 WMH countries (in the United States, Italy, Spain, and France) have provided evidence for a good concordance between CIDI-3.0 diagnoses and diagnoses based on blinded reinterviews, with the area under the receiver operating characteristic curve ranging between .73 and .93 for lifetime mood/anxiety disorders and between .83 and .88 for 12-month mood/anxiety disorders.¹⁶

Frequent or Severe Headaches

The history of frequent or severe headache was ascertained as part of a chronic physical disorder checklist commonly used in national health surveys.³⁰ Respondents were asked whether they had ever had frequent or severe headache, and at what specific age they had it first. Prior research has demonstrated reasonable correspondence between self-reported chronic conditions (eg, diabetes, heart disease, and headache) and records of general practitioners.⁴ However, it was found that chronic pain patients tended to report more pain retrospectively compared to assessments at the time when the pain was actually occurring.²² Moreover, in line with the fact that emotional distress amplifies pain experience, people with emotional problems report a greater intensity of pain compared to those without.^{23,36} Prior research has also shown that it is not so much pain frequency that is subject to recall bias but more likely pain intensity.³²

Statistical Analysis

Discrete-time survival analyses with person-year as the unit of analysis were used to test sequential associations between first onset of mental disorders and the subsequent onset of headache.⁵³ For these analyses, a person-year data set was created in which each year in the life of each respondent up to and including the age of headache onset or their age at interview (whichever came first) was treated as a separate observational record, with the year of headache onset coded 1 and earlier years coded 0 on a dichotomous outcome variable. Mental disorder predictors were coded 1 from the year after first onset of each individual mental disorder. This time lag of 1 year in the coding of the predictors ensured that in cases in which the first onset of a mental disorder and of headache occurred in the same year, the mental disorder would not count as a predictor. Only person-years up to the onset of headache were analyzed so that only mental disorder episodes occurring prior to the onset of headache were included in the predictor set. Logistic regression analyses were used to analyze these data, with the survival coefficients presented as ORs, indicating the relative odds of headache onset in a given year for a person with a prior history of mental disorder compared to a person without that mental disorder (and to people with no mental disorder history). A series of bivariate and multivariate models were developed, including the predictor mental disorder plus control variables. Models control for person-years, country, gender, current age, and, in the multivariate models, also other mental disorders. Bivariate models investigated association of specific mental disorders with subsequent headache onset. The next model, a multivariate model, estimated the associations of each mental disorder with headache onset, adjusting for mental disorder comorbidity (ie, for other mental disorders occurring at any stage prior to the onset of headache). A second multivariate model included a series of predictor variables for number of mental disorders (eg, one such variable for respondents who experienced exactly 1 mental

disorder, another for respondents who experienced exactly 2 mental disorders, and so on), as well as the control variables. Other more complex nonadditive multivariate models were also run—for example, including both type and number of mental disorders—but model fit statistics did not indicate that these provided a better fit for the data, so the simpler models are reported here (the model fitting statistics are available on request).

We examined life course variation in 2 ways. First, we examined whether early- versus late-onset mental disorders differed significantly in their associations with headache onset through the creation of mental disorder-specific dummy variables for early-onset mental disorder (≤ 21 years) and late-onset disorder (> 21 years) (see table footnotes for model specification). Second, we assessed whether associations varied by *when* in the life course headache was reported by including cross-product terms between person-years (coded as a continuous variable) and each type of mental disorder in the multivariate-type model. Gender differences were examined by including cross-product terms between gender and each mental disorder in the multivariate-type model.

Our earlier studies of concurrent mental-physical comorbidity in the WMH surveys found that these associations are generally consistent cross-nationally, despite varying prevalence of mental disorder and physical conditions.⁴⁷ All analyses for this paper were therefore run on the pooled cross-national data set to allow greater reliability of estimates. As the WMH data are both clustered and weighted, the design-based Taylor series linearization implemented in version 10 of the SUDAAN software system, version 8.0.1 (Research Triangle Institute, Research Triangle Park, NC) was used to estimate standard errors and evaluate the statistical significance of coefficients.⁴²

Results

Sample Characteristics and Prevalence Estimates

Table 1 refers to characteristics of the contributing surveys, the number of respondents in Part 1 and 2 of the CIDI-3.0 interview, and prevalence (in both unweighted numbers and weighted percentages) of frequent or severe headaches among respondents (with a total number of 12,371). The overall weighted response rate was 78.0%.

Type and Number of Preexisting Mental Disorders and Their Associations With Subsequent Headache Onset

As shown in Table 2 (first column), bivariate survival models show that all 16 mental disorders included in the analyses are significantly associated with on average 2.2 increased odds (median OR) of subsequent onset of frequent or severe headaches. In particular, impulse-control disorders yielded higher odds than other mental disorders.

In multivariate models that tested the unique associations between preexisting mental disorders and subse-

quent onset of frequent or severe headaches (see Table 2, second column), all ORs decreased, but of the 16 ORs examined, 10 are still greater than 1 and remain statistically significant (with a median significant OR of 1.4). The test of the global null hypothesis was significant ($\chi^2[16] = 798.8, P < .05$), as was the test of whether there is a significant difference between the mental disorder coefficients ($\chi^2[15] = 130.1, P < .05$). This indicates that we are able to identify particular disorders that are associated with headache onset, with IED (OR = 1.9), binge eating disorder (OR = 1.7), and specific phobia (OR = 1.7) as the 3 disorders with the highest odds for developing subsequent headaches.

Multivariate models were estimated that included dummy variables for the number of preexisting mental disorders (Table 2, third column). The ORs in these models can be interpreted as the relative odds of subsequent headache onset among respondents with 1 (or more) preexisting mental disorder versus those without disorders. In general, our data suggest a strong dose-response relationship between the number of preexisting mental disorders and subsequent onset of frequent or severe headaches, with ORs ranging from 1.9 (for 1 preexisting mental disorder) to 3.4 (for ≥ 5 preexisting mental disorders).

Timing of Preexisting Mental Disorders and Their Associations With Subsequent Headache Onset

Bivariate models that investigated the associations between preexisting early- versus later-onset mental disorders and subsequent headache onset (Table 3) showed that early-onset mental disorders had quantitatively larger effects on subsequent onset of headache than later-onset disorders. All preexisting early-onset mental disorders were associated with, on average, a 2.3 increased odds (median OR) of subsequent headache onset. By comparison, the effects of later-onset preexisting mental disorders were slightly different: Only 12 of 16 ORs reached statistical significance, and the overall median OR was lower for later-onset disorders than for early-onset disorders (2.3 vs 1.9, respectively). Among the individual disorders, especially early-onset major depressive episode (MDE)/dysthymia and early-onset panic and phobic disorders had markedly higher odds (ie, 36–38%) of developing frequent or severe headaches.

In the multivariate models that took into account the potential influence of other mental disorders on the investigated associations, a different picture emerged. The most important finding here was that most meaningful differences between early- and later-onset disorders disappeared for about half of the disorders studied. Overall, the median OR of early-onset mental disorders and subsequent headache onset approximated the median OR of later-onset mental disorders and subsequent headache onset (1.6 and 1.4, respectively). However, after controlling for mental disorder comorbidity, there were 3 disorders of which their early-onset variant yielded higher odds than their later-onset variant, and

Table 2. Bivariate and Multivariate Associations (ORs) Between DSM-IV Mental Disorders and the Subsequent Onset of Frequent or Severe Headaches

DSM-IV MENTAL DISORDERS	BIVARIATE MODELS*	MULTIVARIATE-TYPE MODEL†	MULTIVARIATE NUMBER MODEL‡
I. Mood disorders			
MDE/dysthymia	1.9§ (1.8–2.1)	1.4§ (1.3–1.6)	–
Bipolar disorder (broad)	2.4§ (2.0–2.8)	1.3§ (1.1–1.6)	–
II. Anxiety disorders			
Panic disorder	2.2§ (1.9–2.6)	1.3§ (1.1–1.5)	–
Generalized anxiety disorder	2.0§ (1.8–2.3)	1.2§ (1.0–1.3)	–
Social phobia	2.1§ (1.9–2.3)	1.4§ (1.3–1.5)	–
Specific phobia	2.0§ (1.9–2.2)	1.7§ (1.6–1.8)	–
Agoraphobia without panic	2.2§ (1.8–2.8)	1.2 (1.0–1.5)	–
Posttraumatic stress disorder	2.0§ (1.7–2.3)	1.3§ (1.1–1.4)	–
Obsessive compulsive disorder	2.2§ (1.7–2.8)	1.6§ (1.2–2.1)	–
III. Impulse-control disorders			
IED	2.6§ (2.3–3.1)	1.9§ (1.6–2.2)	–
Binge eating disorder	2.4§ (1.7–3.2)	1.7§ (1.2–2.3)	–
Bulimia nervosa	2.2§ (1.7–3.0)	1.2 (.9–1.7)	–
IV. Substance disorders			
Alcohol abuse	1.5§ (1.3–1.7)	1.1 (.9–1.3)	–
Alcohol dependence with abuse	1.7§ (1.5–2.1)	1.0 (.8–1.2)	–
Drug abuse	1.8§ (1.5–2.1)	1.1 (.8–1.3)	–
Drug dependence with abuse	2.3§ (1.8–3.0)	1.2 (.9–1.6)	–
Joint effect of all types of disorders, χ^2_{16}		798.8§	
Difference between types of disorders, χ^2_{15}		130.1§	
V. Number of disorders			
Exactly 1 disorder	–	–	1.9§ (1.8–2.0)
Exactly 2 disorders	–	–	2.5§ (2.3–2.8)
Exactly 3 disorders	–	–	2.6§ (2.2–2.9)
Exactly 4 disorders	–	–	3.0§ (2.4–3.7)
≥5 disorders	–	–	3.4§ (2.8–4.1)
Joint effect of number of disorders, χ^2_5			712.6§

Abbreviation: DSM-IV, *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*.

NOTE. Values are ORs (95% confidence intervals).

*Bivariate models: Each mental disorder type was estimated as a predictor of the physical condition onset in a separate discrete time survival model controlling for age cohorts, gender, person-year, and country.

†Multivariate-type model: The model was estimated with dummy variables for all mental disorders entered simultaneously, including the controls specified above.

‡Multivariate-number model: The model was estimated with dummy predictors for number of mental disorders without any information about type of mental disorders, including the controls specified above.

§Significant at the .05 level, 2-tailed test.

where the ORs reached statistical significance: MDE/dysthymia (33% higher odds of early- vs later-onset variant), social phobia (50% higher odds of early- vs later-onset variant), and specific phobia (42% higher odds of early- vs later-onset variant).

Preexisting Mental Disorders and Their Associations With Timing of Subsequent Headache Onset During the Life Course

A next set of analyses investigated the strength of the associations between preexisting mental disorders and when in life respondents actually developed their frequent or severe headaches. Except for obsessive-compulsive disorder and binge eating disorders, the mental disorder × person-year interaction test was significant ($P < .05$) for all mental disorders. These significant interactions indicate that the effects of preexisting mental disorders vary significantly over the life course and that for most disorders associations were stronger between preexisting mental disorders and

headaches when headache onset occurred earlier in life (Table 4). Of interest was that in contrast to the rest of the disorders studied, MDE/dysthymia, specific phobia, and IED appeared to have a lifelong influence on headache onset, suggesting that the influence of these disorders may thus be more pervasive than that of other disorders.

Gender Differences in the Associations Between Preexisting Mental Disorders and Subsequent Onset of Frequent or Severe Headaches

A final research question pertained to the question whether we could find gender differences. We found only 1 significant effect: The association between generalized anxiety disorder and frequent or severe headache was weaker for female respondents (compared to male respondents; interaction OR = .7; 95% confidence interval = .5–.7; $P = .010$). No other gender differences were found.

Table 3. Associations (ORs) Between Early Versus Late Mental Disorder Onset and the Subsequent Onset of Frequent or Severe Headaches

MENTAL DISORDER	BIVARIATE MODELS*			MULTIVARIATE MODEL†		
	EARLY	LATE	TEST OF THE DIFFERENCE BETWEEN EARLY AND LATE χ^2_1 [P]	EARLY	LATE	TEST OF THE DIFFERENCE BETWEEN EARLY AND LATE χ^2_1 [P]
I. Mood disorders						
MDE/dysthymia	2.4‡ (2.2–2.6)	1.5‡ (1.3–1.6)	57.0‡ [.000]	1.6‡ (1.5–1.8)	1.2‡ (1.1–1.4)	16.0‡ [.000]
Bipolar disorder (broad)	2.4‡ (2.0–2.9)	2.4‡ (1.7–3.3)	.0 [.968]	1.2 (.9–1.5)	1.4 (1.0–2.0)	.7 [.395]
II. Anxiety disorders						
Panic disorder	2.6‡ (2.2–3.2)	1.6‡ (1.3–2.1)	9.2‡ [.003]	1.4‡ (1.1–1.8)	1.1 (.8–1.4)	2.5 [.112]
Generalized anxiety disorder	2.3‡ (2.0–2.7)	1.7‡ (1.4–2.1)	6.7‡ [.009]	1.2 (1.0–1.4)	1.2 (1.0–1.4)	.0 [.938]
Social phobia	2.2‡ (2.0–2.4)	1.0 (.7–1.5)	15.2‡ [.000]	1.4‡ (1.3–1.5)	.7‡ (.4–1.0)	13.2‡ [.000]
Specific phobia	2.1‡ (1.9–2.2)	1.3 (.9–1.9)	6.3‡ [.012]	1.7‡ (1.6–1.8)	1.2 (.8–1.7)	4.5‡ [.033]
Agoraphobia without panic disorder	2.3‡ (1.8–2.9)	1.9‡ (1.1–3.3)	.5 [.492]	1.2 (1.0–1.6)	1.2 (.7–2.2)	.0 [.980]
Posttraumatic stress disorder	2.3‡ (2.0–2.7)	1.5‡ (1.2–2.0)	7.4‡ [.007]	1.3‡ (1.1–1.5)	1.1 (.8–1.4)	1.9 [.173]
Obsessive compulsive disorder	2.1‡ (1.6–2.8)	2.5‡ (1.6–4.0)	.5 [.470]	1.6‡ (1.2–2.1)	1.7‡ (1.0–2.7)	.1 [.782]
III. Impulse-control disorders						
IED	2.7‡ (2.3–3.2)	2.5‡ (1.9–3.3)	.2 [.638]	1.9‡ (1.6–2.2)	1.8‡ (1.3–2.5)	.0 [.853]
Binge eating disorder	2.2‡ (1.6–3.1)	2.6‡ (1.5–4.8)	.3 [.592]	1.6‡ (1.1–2.2)	1.8‡ (1.0–3.3)	.2 [.679]
Bulimia nervosa	2.3‡ (1.7–3.3)	1.9 (1.0–3.5)	.4 [.534]	1.2 (.8–1.7)	1.3 (.7–2.4)	.0 [.897]
IV. Substance disorders						
Alcohol abuse	1.7‡ (1.5–2.0)	1.2 (1.0–1.4)	11.4‡ [.001]	1.2 (1.0–1.5)	.9 (.8–1.2)	4.1‡ [.042]
Alcohol dependence with abuse	1.8‡ (1.5–2.3)	1.6‡ (1.2–2.1)	.7 [.397]	.8 (.7–1.1)	1.1 (.8–1.5)	2.4 [.124]
Drug abuse	1.8‡ (1.5–2.2)	1.7‡ (1.2–2.6)	.0 [.901]	1.0 (.8–1.3)	1.2 (.8–1.8)	.7 [.402]
Drug dependence with abuse	2.5‡ (1.8–3.4)	1.9‡ (1.2–3.0)	1.2 [.272]	1.3 (.9–1.9)	.9 (.6–1.4)	1.4 [.236]
V. Joint effect of all early-onset disorders, χ^2_{16}				764.2‡		
VI. Joint effect of all late-onset disorders, χ^2_{16}					64.8‡	
VII. Joint effect of early onset disorders independent of joint effect of any disorders, χ^2_{16}						56.3‡

Abbreviation: CI, confidence interval.

*Models include dummy variables for early-onset mental disorders (= first onset <21 years of age) and for late-onset disorders, plus control variables (age cohort, person years, gender, and country). A second bivariate model was estimated to test the significance of the difference between early and late-onset disorders. This model included the dummy variables for the early-onset disorder and the dummy variable for the disorder itself (ie, having it at all), plus controls.

†Multivariate models paralleled the bivariate models in design but included dummy variables for all mental disorders entered simultaneously.

‡Significant at the .05 level, 2-tailed test.

Discussion

Associations Between Preexisting Mental Disorders and Subsequent Onset of Headaches

This paper reports the first large-scale, cross-national assessment of the temporal relationship between retrospectively reported preexisting common mental disorders and the subsequent onset of headaches in general population samples worldwide. In bivariate analyses, virtually all preexisting mental disorders were associated with subsequent headache onset. After adjusting for influences of gender, age, and mental disorder comorbidity, we found that a broad spectrum of mental disorders (such as mood, anxiety, and impulse-control disorders) increased the odds of developing subsequent frequent or severe headaches by on average 40%, with IED (OR = 1.9), binge eating disorders (OR = 1.7), and specific phobia (OR = 1.7) as individual disorders with the strongest associations, even after adjusting for mental disorder comorbidity. Although these

findings need to be confirmed in prospective studies, in general they support the antecedent hypothesis of the development of mental/physical comorbidity that posits that people with mental disorders may be more vulnerable to headaches that develop after the mental disorder onset.¹³ More specifically, temporal relationships between phobia and depression with subsequent headache onset have been described in prior research, but the specific effects of impulse control disorders have not been reported before.^{8,26,39} This could be due to the fact that previous studies simply did not include this group of disorders as potential risk factors for onset of headaches. In particular, IED, either as a single or comorbid condition, was associated with an almost 2-fold increased risk of subsequent headache onset, and our data also suggest that this association remains fairly stable throughout the life course. This means that IED, either pure or comorbid, appears to be a disorder that is strongly bound with headache onset at any time in life. This is a novel finding: IED has never before been found to be a psychological

Table 4. Variations in Associations Between Mental Disorders and Frequent or Severe Headaches by Life Course Timing of Headache Onset

TYPE OF MENTAL DISORDERS*	MENTAL DISORDER × PERSON-YEAR INTERACTION†		STRATIFIED MODELS‡			
	OR (95% CI)	χ ₁ ² [P]	UP TO AGE 17	AGE 18–25	AGE 26–38	AGE ≥39
MDE/dysthymia	.97§ (.97–.98)	79.6§ [.000]	2.0§ (1.6–2.5)	1.7§ (1.5–2.0)	1.4§ (1.2–1.6)	1.7§ (1.4–2.0)
Bipolar disorder (broad)	.97§ (.96–.99)	9.0§ [.003]	1.9§ (1.3–2.8)	1.0 (.7–1.3)	1.5§ (1.1–2.1)	1.5 (1.0–2.4)
Panic disorder	.98§ (.97–.99)	15.7§ [.000]	1.2 (.8–1.8)	1.6§ (1.2–2.1)	1.4§ (1.1–1.8)	1.4§ (1.0–1.9)
Generalized anxiety disorder	.98§ (.97–.99)	21.8§ [.000]	1.3 (.9–1.7)	1.1 (.9–1.4)	1.4§ (1.1–1.7)	1.3 (1.0–1.6)
Social phobia	.97§ (.96–.97)	71.3§ [.000]	1.4§ (1.1–1.8)	1.3§ (1.1–1.5)	1.2 (1.0–1.5)	1.2 (.9–1.6)
Specific phobia	.98§ (.97–.98)	97.3§ [.000]	1.9§ (1.7–2.1)	1.4§ (1.2–1.6)	1.6§ (1.4–1.8)	1.5§ (1.2–1.8)
Agoraphobia without panic	.98§ (.96–.99)	9.4§ [.002]	1.2 (.7–2.1)	1.6§ (1.1–2.4)	.8 (.6–1.2)	1.6§ (1.1–2.4)
Posttraumatic stress disorder	.97§ (.96–.98)	43.1§ [.000]	1.4§ (1.1–1.8)	1.5§ (1.2–1.9)	1.3 (1.0–1.7)	1.2 (.9–1.7)
IED	.98§ (.97–1.00)	5.1§ [.023]	1.8§ (1.4–2.4)	1.9§ (1.5–2.4)	1.7§ (1.3–2.3)	1.8§ (1.3–2.6)
Alcohol abuse	.98§ (.97–.99)	14.0§ [.000]	1.0 (.5–1.7)	1.2 (.9–1.5)	1.3§ (1.0–1.6)	1.2 (.9–1.6)
Alcohol dependence with abuse	.98§ (.96–1.00)	5.1§ [.024]	.7 (.3–1.5)	1.0 (.7–1.4)	1.0 (.7–1.4)	1.1 (.7–1.6)
Drug abuse	.97§ (.95–.98)	12.5§ [.000]	1.6 (.8–3.3)	.9 (.6–1.4)	1.4 (.9–2.0)	1.1 (.6–1.7)
Drug dependence with abuse	.96§ (.92–.99)	5.2§ [.022]	1.1 (.5–2.4)	1.9§ (1.2–3.1)	.7 (.4–1.2)	1.1 (.5–2.5)

Abbreviation: CI, confidence interval.

*Only disorders with significant gender × age interactions are provided.

†A series of multivariate models were estimated. For example, the model for depression included the dummy variables for all mental disorders plus the cross-product term for depression and person-year (as a continuous variable), plus the controls specified for earlier models.

‡The multivariate model was estimated in the 4 person-year data sets corresponding to quartiles of the frequent or severe headache-onset distribution.

§OR significant at the .05 level, 2-sided test.

correlate or precursor of headache in clinical or general adult population samples. Interestingly, some studies with pediatric samples showed not only that impulsive symptoms were comorbid with chronic headaches (with ORs in the 2.1–2.6 range) but also that they preceded the onset of headaches among 4- to 10-year-olds.^{5,6} Although this finding needs further exploration, it could be that anger is the underlying construct that might explain the observed association between IED and headache.³¹ We do not have a conclusive explanation why exactly IED, specific phobia, and binge eating disorder are among the most important predictors of later-life chronic headaches, but the fact that all 3 disorders are typically early-onset disorders suggests that they might be useful young-age markers for progression to later somatic conditions. It is interesting that some other analyses of the same data set also found impulsive disorders to be predictive of other later-life chronic somatic conditions such as ulcer, diabetes, and hypertension.^{40,44} This points to a potential temporal effect between impulsive behaviors/symptoms and the onset of several, and not just one specific, chronic somatic condition. In addition, our results are consistent with some studies apparently not showing a relationship between substance abuse and migraine.³⁷ Indeed, our data are not consistent with those showing that the presence of substance use disorders—although they are often-times seen as impulsive behaviors—increased the odds of subsequent chronic headache onset.^{1,35,55} As noted above, because of the cross-sectional design, our data cannot be interpreted as conclusive but rather as exploratory, and hence further study is necessary to confirm or refute these associations.

The Temporal Effects in the Association Between Preexisting Mental Disorders and the Onset of Chronic Headaches

We not only found that respondents with preexisting mental disorders yielded approximately 2-fold higher odds of subsequent onset of headaches compared to those without preexisting disorders, but also found that among those with a mental disorder, persons with early-onset disorders (ie, onset prior to the age of 21) had an additional 21% higher odds of developing headaches than persons with later-onset mental disorders. After controlling for mental disorder comorbidity (in multivariate analyses), the effects of early- versus later-onset disorders disappeared for most mental disorders. This indicates that the stronger associations between early-onset mental disorders and subsequent headaches is largely due to early-onset mental disorders, being risk markers or risk factors for mental disorder comorbidity.

However, some early-onset disorders (eg, MDE/dysthymia, social phobia, and specific phobia) were systematically more strongly associated with headache onset than their later-onset variant, even after comorbidity adjustment. Indeed, even after taking out the effect of the comorbidity that goes with early disorders, they are still more strongly associated with subsequent headache than their later variants. This suggests that for these 3 disorders, the earliness of onset timing itself (prior to 21 years) may increase the odds of headache onset. A possible explanation is that these early disorders, when they occur at a critical period in the young person’s development, may be associated with stress-provoking emotions and cognitions involving shared neurobiologic and neuroendocrine mechanisms, such as hypothalamic-pituitary-adrenal axis

overactivation and dysregulated stress response pathways.^{14,54} Subsequently, this may increase the risk of not only headaches but also other somatic problems. Evidence of this kind has already been reported for depression, but our data suggest that this mechanism may also be worth exploring with phobias.⁴⁹

Clinical Implications

From a perspective of clinical relevance, our study has 3 notable findings that may warrant some attention. First, we have found that mental disorder comorbidity is important because it increases headache onset risk. In light of the fact that mental disorder comorbidity is the rule rather than the exception, clinicians should be aware of this strong association.²⁰ This implication is important for mental health professionals because of our finding that mental disorder comorbidity precedes later onset of headaches. But maybe this finding is even more important for general practitioners, as persons with chronic headaches are more likely to consult general medicine practitioners than specialized mental health professionals. Given that mental disorders are chronic and persistent, it is particularly important that general medicine professionals be aware of the fact that mental disorder comorbidity is associated with the onset of frequent/severe headaches and that this relationship may have a chronic character. Second, a large number of specific mental disorders remained associated with subsequent headache after adjusting for comorbidity. This demonstrates the overall strong relationship between mental disorders and chronic headache onset, but this finding also points to the need to broaden the focus beyond depression. In particular, impulse control disorders may increase the risk of subsequent headache onset. Third, in both bivariate and multivariate models, we found that respondents with early-onset MDE/dysthymia, social phobia, and specific phobia were more likely to develop headaches compared to respondents with a later-onset variant of these disorders. In particular, these may be seen as disorders that may be a target of preventive efforts that are aimed to reduce the large burden of pain conditions, especially when they occur early in life.

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Limitations of the Study

A first limitation relates to the sampling methodology. Although we investigated temporal associations between mental disorders and the subsequent onset of headache, our study was retrospective and so subject to possible inaccuracies in the temporal sequence of mental disorders and headaches. Further, the observational nature of the study means that we cannot draw firm conclusions with regard to potential causal effects between preexisting mental disorders and the onset of headache. Further prospective research should therefore focus on ages of onset of mental disorders and headache problems in order to gain more knowledge on the course of comorbid mental disorders and this pain condition. A second limitation pertains to the assessment of frequent or severe headaches and mental disorders. The assessment of headaches was based on a single question from the National Health Interview Survey asking for the history of frequent or severe headaches without gathering detailed information regarding headache subtypes, chronicity, or frequency of headache attacks.⁸ With regard to the assessment of mental disorders, the prevalence estimates of lifetime mental disorders (and mild disorders in particular) are likely to be underreported and biased in accuracy in the reported ages of onset.^{43,51} A third limitation is that we used a restricted set of common mental disorders in the analyses. A number of burdensome disorders, such as dementia and psychosis, were not included. Nonetheless, the disorders we did consider included many of those most commonly reported in previous population studies.²⁹ Further study should focus more closely on possibly high-impact disorders that were not included in the present study.

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