

Humanistic and Economic Burden of Depression and Anxiety among Adults with Migraine: A systematic review

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Research article

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Abstract

Background Depression and anxiety are highly prevalent disabling chronic conditions among adults with migraine. These comorbid conditions are becoming a well-recognized public health problem in many countries due to their humanistic and economic burden. **Objectives** This review was conducted to assess systematically the humanistic and financial burden of migraine and depression and/or anxiety disorder among adults with migraine.

Methods A systematic literature search conducted using MedLine and CINAHL via EBSCO, OVID and Cochrane Database of Systematic Reviews via OVID. Studies evaluating the humanistic burden (disability and Health-related Quality of Life (HRQoL)) and the economic burden and healthcare utilization of comorbid depression and anxiety among adults with migraine that were published in peer-reviewed English language journals from inception until August 2019 were included.

Results Of the 957 articles identified, 24 studies were included in the review. HRQoL was measured using generic, and migraine-specific measures. Regarding the humanistic burden, twelve studies reported an association between depression and/or anxiety and lower HRQoL and seven studies reported an association between depression and/or anxiety and higher disability. Regarding the economic burden, only two studies were identified and both found that depression and/or anxiety are associated with higher healthcare expenditures and utilization among adults with migraine.

Conclusions These results of this review highlight the substantial impact of depression and/or anxiety on HRQoL, disability, healthcare cost and utilization of medical services for adults with migraine. It is important for healthcare providers to be aware of the negative impact of these illnesses and identify and treat anxiety and depression as treatment may have a potential to improve the health outcomes of patients living with migraine.

Background

Depression and anxiety are highly prevalent among adults with migraine. Adults with migraine are two to four times more likely to suffer from depression and anxiety compared to adults in the general population [1-4]. Worldwide, migraine and depression are one of the top five disabling conditions measured as years lived with disability (YLDs) [5]. The American Migraine Prevalence and Prevention (AMPP) Study among 19,189 adults with migraine have documented that adults suffering from chronic migraine had a greater migraine-related disability than those with episodic migraine [6]. Coexisting depression and anxiety among adults with migraine are not only a major clinical problem but they are associated with higher disability [7], and poor Health-Related Quality of Life (HRQoL) [1, 7, 8]. A population-based studies in the United States (U.S.) and the United Kingdom reported that subjects with migraine have a significantly lower score of HRQoL in two domains; the mental and physical health component scores due to comorbidity of migraine and depression that each exerts a significant effect on HRQoL [1].

Further, as the result of the combined disability, depression and anxiety is likely to affect healthcare costs and utilization [9, 10]. Migraine is one of the most expensive chronic conditions, with an estimated annual cost of

\$17 billion in the U.S. alone [11]. Depression and anxiety among adults with migraine lead to significantly greater healthcare costs [9, 10]. Yet, depression and anxiety are unrecognized and untreated in adults with migraine [3]. This is partially attributed to the competing demand to treat migraine coupled with the overlap of the symptoms of depression and migraine (e.g., insomnia).

The purpose of this review is to assess the humanistic and financial burden of migraine and comorbid depression and/or anxiety disorder among adults with migraine. Our research questions can be summarized as:

1. Does coexisting depression and/or anxiety affect the HRQoL and disability of adults with migraine?
2. Does coexisting depression and/or anxiety affect the healthcare costs and utilization of adults with migraine?
3. Have the aforementioned questions been sufficiently addressed in the literature and what future research is needed in these areas?

By summarizing a large body of literature it should be possible to reach a more broad understanding of both the current evidence and the most appropriate directions for future research in this area.

Method

Design

The Preferred Reporting Items for the Systematic Reviews and Meta-Analyses (PRISMA) guideline was used to guide the conduct of the present systematic review.[12]

Search Strategy

The comprehensive systematic review presented below is based on computerized systematic literature conducted using three databases (MedLine and CINAHL via EBSCO, and Cochrane Database of Systematic Reviews via OVID). Articles were also identified by a manual search of bibliographies from all retrieved articles. This review attempted to identify all studies that cover the humanistic and economic outcomes of coexisting depression and anxiety among adults with migraine that were published in English in peer-reviewed journals from inception until August 2019. The search strategy used the Medical Subject Headings (MeSH) terms and keywords relating to depression, anxiety, migraine, disability, HRQoL, and healthcare cost and utilization for each database. The following combinations of keywords were searched:

1. Anxiety or depression
2. Health-related quality of life (HRQoL) or disability or healthcare cost or healthcare utilization
3. Migraine

Abstracts and articles were read for relevance to the research questions. Articles were included in the review if they met the following criteria: used validated measure to diagnose migraine, used validated self-report measures of HRQoL and disability; used validated diagnostic measures of depression and anxiety with

clinical or threshold score; sample includes adults (i.e. not pediatric populations); assess either humanistic burden (disability, HRQoL) and/or economic burden (direct or indirect healthcare costs or healthcare utilization). Articles which did not meet the above criteria were excluded. Conference abstracts and full-text articles without raw data available for extraction were excluded. Figure 1 shows how the database search and article selection process resulted in twenty-one articles being included in this review. Details on the specific search terms and their combinations are provided in Appendix I. Database search was conducted independently by the author and a research assistant, with further confirmation of search strategy by a second research assistant.

Study Selection

The initial literature screening involved examining the titles and abstracts of extracted articles for potential relevance for inclusion by the author and an independent research assistant. Full-text studies potentially related to the review questions were then assessed against the inclusion/exclusion criteria independently by the author and the research assistant and any disagreements were discussed and resolved by the second research assistant.

Data Extraction and Analysis

The author and the research assistant independently extracted the included data. Study characteristics (author and year of publication), methodological details (study design, location, study participants, sample size, mean age, and percentage women), main outcome measures, and findings were extracted from our eligible articles and entered into a Microsoft Excel® spreadsheet designed to facilitate data sorting and assessment of study quality.

Quality Assessment

The included studies were assessed for their quality using the Appraisal Tool for Cross-Sectional Studies (AXIS tool) [13]. The author and the research assistant independently performed a quality assessment for each included study. This tool contains twenty criteria for three domains: 1) quality of reporting; 2) study design quality; and 3) introduction of biases in the study. For each criterion met, the study received one point; the maximum score is twenty indicates the highest quality of the included study in the present review.

Results

Selection Process

A total of 640 articles were identified from all searches. Based on the title and abstract screening, 48 full-text articles were retrieved. Of these, 24 studies met the inclusion criteria and included in the final review (Figure 1).

General Characteristics of Included Studies

The description of the included studies is displayed in Table 1, 2 & 3. Although there were no limitations on the year of publication, studies only started to emerge since 2000. Nineteen studies examined the humanistic burden, twelve examined HRQoL [1, 7, 14-24] and seven examined disability [7, 17, 24-28] and two studies assessed the economic burden, three studies examine the healthcare cost [9, 29, 30] and medical services utilization [4, 29]. All studies employed validated measures of migraine, HRQoL, depression, and anxiety. The total number of included participants was 26,967 with sample sizes ranging from 70 to 11,332. In general, the participants' age ranged from 18 to 75 years, with women percentages ranging from 51.0% to 100%. Many studies included mixed-sex but two studies [20, 24] exclusively investigated women.

Quality Assessment

Overall, the included studies scored well for clearly stating the study aims, design, target population, risk factors and outcomes measurement, result explanation, and discussion and conclusion justified by the results. The main issues were mainly related to failure to address the sample calculation or addressing the non-response rate.

Main Findings

For this review, the results have been categorized into humanistic (Table 1&2) and economic burden (Table 3).

Depression and or Anxiety Comorbidity

Depression and anxiety were mainly evaluated using the Beck Depression Inventory (BDI) in four studies. Other scales were also used such as Hospital Anxiety and Depression Score (HADS), Patient Health Questionnaire-4 (PHQ-4), and the Center for Epidemiologic Studies-Depression Scale.

Humanistic Burden of Comorbid Depression and Anxiety among Adults with Migraine

The humanistic burden was measured using the HRQoL and disability. HRQoL instruments evaluate the burden of a disease on a person's overall well-being [31]. Twelve studies gave data for the HRQoL outcome for adults with migraine and comorbid depression and/or anxiety. The results from these studies showed that depression and/or anxiety had a negative impact on the HRQoL. HRQoL instruments used were either generic or disease-specific. Most studies mentioned in this review that assessed the HRQoL among individuals with

migraine used generic instruments (Table 1). The generic HRQoL instruments included: 36-item Short Form Health Survey (SF-36), the 12-item Short Form Health Survey (SF-12). The Short-Forms measures HRQoL in two domains: a mental health component score (MCS-12) and a physical health component score (PCS-12). The disease-specific HRQoL measure, Migraine-Specific Quality-of-Life Questionnaire (MSQ), was used in five studies.

A national population-based study in Canada using a national data from the Canadian Community Health Survey evaluated the impact of depression or anxiety on HRQoL [22]. This study found that among adults with migraine; those with depression or anxiety had lower HRQoL compared to those without these conditions. Studies in China, France, Germany, Italy, India, and South Korea have also demonstrated poor HRQoL among individuals with migraine and depression and/or anxiety [15, 18, 19]. A nation-wide population-based survey in France among subjects with migraine (n=1,957), in which 28.0% had anxiety, 3.5% depression, and 19.1% had both conditions [7]. The investigators reported that subjects with anxiety only, depression only or combined with depression had significantly lower scores across all domains of the SF-12 scale than in subjects with neither anxiety nor depression. To summarize, poor HRQoL among adults with migraine was explained by depression and /or anxiety comorbidity in most of the studies compared to groups without these comorbidities.

Disability is a measure of disease burden. Seven studies gave data for the disability outcome for adults with migraine and comorbid depression and/or anxiety (Table 3). The results from the studies included in this review showed that depression and anxiety had a negative impact on the disability using either generic (e.g., World Health Organization Disability Assessment Schedule II) or disease-specific (e.g., Migraine Disability Assessment) measures. Seng et al. in their study among adults with migraine have used migraine-specific measure, Migraine Disability Assessment (MIDAS), to measure disability associated with mental health conditions [25]. The researchers found that a higher depressive symptoms (Odds Ratio (OR) =3.5, 95%CI: 1.4-8.4), or anxiety symptoms (OR =3.6, 95% CI: 1.6-8.0) were associated with severe migraine-related disability. In summary, depression and anxiety have been associated with higher disability among adults with migraines when compared to those without these comorbidities.

Economic Burden of Comorbid Depression and Anxiety among Adults with Migraine

Economic burden was measured using the healthcare cost and healthcare utilization. Three studies gave data for the healthcare cost and the healthcare utilization outcomes for adults with migraine and comorbid depression and/or anxiety. With regard to healthcare costs, depression and/or anxiety comorbidity can exacerbate the economic burden of the payers. The economic burden was measured with the direct medical costs related to medical resource utilization of inpatient, outpatient and pharmaceutical services for treating adults with migraine. The current evidence among adults with migraine reported that individuals with comorbid depression and/or anxiety have higher healthcare costs [9, 29, 30] and medical services utilization[29] than those without these comorbid mental health conditions.

Pesa et al. examined the direct healthcare cost of comorbid depression and/or anxiety among individuals with migraine using retrospective employer database [9]. The investigators found that the mean annual total healthcare costs for coexisting depression and/or anxiety along with migraine were higher when compared to migraine alone ($P < .0001$) (\$12,642 vs \$5,179 anxiety; \$11,290 vs \$3,135 depression). Wu et al. examined the direct healthcare costs of comorbid depression and/or anxiety among individuals with migraine using retrospective Medical Expenditures Panel survey of US adults [29]. They reported that migraine subjects with depression have a higher mean annual total health expenses (\$10,012 vs. \$4,740, $P < .001$) and mean migraine-related health expenses (\$723 vs \$499, $P = .014$) compared to those without depression.

Further, comorbid depression and or anxiety significantly affected healthcare utilization patterns. Wu et al. reported a higher odds of emergency department visit in adults with migraine and comorbid depression compared to those without depression (OR=1.36, 95% CI: 1.08, 1.71) [29]. This study suggests that depression increases healthcare utilization among adults with migraine, however, the impact of anxiety alone or comorbid depression and anxiety on healthcare utilization not been evaluated yet.

Discussion

The present review highlights the substantial disease burden of comorbid depression and/or anxiety among adults with migraine in terms of HRQoL, disability, and healthcare costs and utilization. Consistent evidence from the included studies on the impact of depression and/or anxiety comorbidity on humanistic and economic burden among adults with migraine was found. Twenty-one studies were identified, predominately evaluated the humanistic burden.

When the humanistic burden of depression and/or anxiety among adults with migraine was measured using either a generic or a disease-specific measure of HRQoL, studies were consistent in documenting a relationship between the presence of either of these conditions and poor HRQoL [1, 7, 14–24]. In some studies, these illnesses affect both the mental and physical health component scores of HRQoL.[1] However, many studies have found a greater negative impact on mental health component [1, 7, 17, 19, 23], than the physical components reinforcing that mental health is a substantial concern for patients with migraine. Most of the studies have been focused on depression comorbidity, however, anxiety usually coexist with depression and this segment of the population may have a more negative outcome than individuals with migraine and depression, therefore, future studies on the impact of depression and anxiety comorbidity on HRQoL are warranted.

Further, when the burden of depression and/or anxiety was evaluated in terms of disability, studies reported a consistent relationship with higher disability [7, 17, 24–26]. However, the definitions of disability varied among studies. Most of the studies used the Migraine Disability Assessment scale. Only two studies examined the relationship between anxiety and migraine-related disability [25] and no studies have examined the impact of anxiety and depression comorbidity on the disability of adults with migraine. In all included studies, depression and anxiety were both associated with severe migraine-related disability. Lanteri-Minet et al. in their study among 1,834 adults with migraine using data from the FRAMIG 3, national population-based survey for migraine in France, have found that the migraine-related disability was associated with anxiety-depression comorbidity but not with either disease alone [7]. Despite the substantial impact of depression

and/ or anxiety on disability, a further investigation of the impact of mental disorders on disability using a multicenter, longitudinal and large sample size is worth exploration.

The current evidence among adults with migraine reported that individuals with comorbid depression and/or anxiety have a higher economic burden in terms of healthcare costs and medical services utilization [9, 10]. Only three studies estimated the excess economic burden of depression and/or anxiety among individuals with migraine. These studies found that that direct medical care costs were higher for those with depression and/or anxiety. In terms of healthcare utilization, only one study identified in this review was used a large national U.S. data, this study have reported that adults with migraine and depression have a significantly higher hospitalizations (16.5 vs 8.6), all-cause emergency department visits (13.8 vs 7.1), all-cause office visits (13.8 vs 7.1), prescription drug use (35.2 vs 12.6) compared to those without depression [29]. The higher healthcare utilization could be due to that depression may exacerbate migraine symptoms and increase the need for healthcare utilization and migraine treatment. This is supported by the findings from SMILE study that was conducted in France among 5,417 migraine patients from primary care which have shown an elevated utilization of acute treatment of migraine among patients with co-existing anxiety and depression [32].

Given the higher economic and humanistic burden of disability and HRQoL among adults with migraine and the higher mental comorbidity, information on patient-mental health is poorly diagnosed at the office visits. Minen et al in their study among primary care physicians (PCPs) have found that one-third of PCPs do not routinely assess depression and about half of the physicians do not routinely screen for anxiety [33]. The findings from this review support the need for regular screening tools for mental health as part of comprehensive clinical care for adults with migraine. Adults with migraine may benefit from routine mental health screening to capture the mental health of patients early before it affects the health outcomes of adults with migraine.

This systematic review utilized a vigorous search strategy to summarize the current knowledge on the humanistic and economic burden of coexisting depression and anxiety among adults with migraine. Although the qualities of the included studies were evaluated, the results should be interpreted with caution considering some limitations from each included studies. First, there was no consistency in defining cases of depression or anxiety from different studies. For example, some studies defined depression or anxiety as symptomology and others that have used a threshold to define probable cases of depression or anxiety. Second, several factors are known to influence both HRQoL and the healthcare costs and utilization such as the severity of migraine, migraine-related disability, and income have not been taken into account by adjusting for them in the analyses in many studies. These factors may affect the association between depression or anxiety and the humanistic and economic burden. However, the studies that adjusted for these confounders did not change the association between depression or anxiety and the health outcomes for adults with migraine. However, confounders can affect the estimates and therefore provide biased estimates and should be therefore adjusted in the analysis. Third, is the generalizability of the included studies, many studies have recruited subjects from a single headache centre and it is likely to and it is likely to be descriptive only of the most severe migraine, Therefore, a population-based study to measure the impact of depression and anxiety on the humanistic and economic outcomes of subjects with migraine is needed.

Conclusions

In summary, this review documents an association between depression and anxiety and the humanistic and economic outcomes of subjects with migraine. Both depression and anxiety are associated with poorer humanistic and economic outcomes including decreased health related quality of life, and increased disability and healthcare utilization and cost. These findings emphasize the importance of screening and treatment of mental health disorders for adults with migraine to reduce the burden on the payer, patients, and healthcare system.

Abbreviations

YLDs years lived with disability, AMPP American Migraine Prevalence and Prevention Study, HRQoL Health-Related Quality of Life, U.S. United States, PRISMA Preferred Reporting Items for the Systematic Reviews and Meta-Analyses, MeSH Medical Subject Headings, AXIS tool Appraisal Tool for Cross-Sectional Studies, BDI Beck Depression Inventory, HADS Hospital Anxiety and Depression Score, PHQ-4 Patient Health Questionnaire-4, SF-36 36-item Short Form Health Survey, SF-12 12-item Short Form Health Survey, MCS-12 mental health component score, PCS-12 physical health component score, MSQ Migraine-Specific Quality-of-Life Questionnaire, MIDAS Migraine Disability Assessment, OR Odds Ratio, PCPs primary care physicians.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

Not applicable.

Competing interests

The author declares that there are no conflicts of interest regarding the publication of this paper.

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Author contributions

MA has full access to the data in the study, has been responsible for the study concept and design, drafting the manuscript, acquisition of data, interpretation of data, final approval of the version to be published and takes responsibility for the integrity of the data and accuracy of the data. NM and AO have contributed to the data reported in the article but does not fulfill authorship criteria. No compensation was received for such contributions.

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Tables

Table 1: Characteristics of Included Studies that Measures Health Related Quality of Life

Author (Publication Year)	Country	Study Design and Participants	Sample Size (n)	Average age year, M(SD)	% Women	Migraine Measures	Depression Measures	Anxiety Measures	HRQoL Measures	Main Findings
Prisnie JC (2018)[14]	Canada	Cross-sectional study, subjects were recruited from outpatient neurology clinics	268	42.8 (13.3)	80%	Physician diagnosis	PHQ-9	HADS-A	SF-12	Anxiety and depression were associated with decrease in HRQoL (physical and mental health components)
Wang et al. (2016)[15]	China	A community-based Cross-sectional study-Survey	1,143	44.8 (15.68)	84%	ID Migraine	BDI		SF-36	Depression was associated with decrease in HRQoL (physical role domain)
D'Amico et al. (2015)[16]	Italy	Cross-sectional study, subjects were recruited from Headache Centre	194	43.9	83%	Physician diagnosis	BDI		MSQoL	Depression was associated with decrease in HRQoL
Dindo et al. (2015)[17]	US	Cross-sectional study, participants recruited for a clinical trial	93	32.0 (13.0)	89%	ID Migraine	Structured Clinical Interview for DSM-IV		SF-36	Depression was associated with decrease in HRQoL (physical and mental health components)
Kim et al. (2014)[18]	South Korea	Cross-sectional study, subject recruited from a headache clinic	251	41.4 (13.4)	88%	ICHD-2	BDI	BAI	MSQoL	Depression was associated with decrease in HRQoL
Sharma et al. (2013)[19]	India	Cross-sectional study, subject recruited from a headache clinic	71	30.6 (9.1)	79%	ICHD-2	HADS	HADS	SF-26	Anxiety and depression were associated with decrease in HRQoL (physical and mental health components)

Table 1: Characteristics of Included Studies that Measures Health Related Quality of Life

Author (Publication Year)	Country	Study Design and Participants	Sample Size (n)	Average age year, M(SD)	% Women	Migraine Measures	Depression Measures	Anxiety Measures	HRQoL Measures	Main Findings
Stuginski-Barbosa et al. (2012)[20]	Brazil	Cross-sectional study, women were recruited from outpatient headache service with episodic and chronic migraine	179	38.6	100%	ICHD-2	BDI		SF-36	Depression was associated with decrease in HRQoL
Jette N et al. (2008)[22]	Canada	Canadian Community Health population-based study, subjects with migraine	3984		73%	Subjects were asked "Do you have migraine headaches?"	WMH-CIDI	WMH-CIDI	SF-36	Depression and anxiety are associated with decrease in HRQoL
Brna P et al. (2006)[23]	Canada	Cross-sectional study	699	44	51%	All respondents were asked, "Do you have migraine headaches?"	Asking subjects and validating against medication use or visits with mental health professional	Asking subjects and validating against medication use or visits with mental health professional	SF-36	Anxiety disorder was associated with decrease in HRQoL in 6/8 domains.
Lanteri-Minet et al. (2005)[7]	France	Cross-sectional population-based study among adults with active migraine	1,957	41.9 (14.5)	70%	ICHD-2	HADS	HADS	SF-12	Anxiety only, depression only, or both anxiety and depression were associated with decrease un HRQoL
Kolotylo et al. (2000)[24]		Cross-sectional mailed survey for women	247	43.4	100%	ICHD-2	CESD		MSQoL	Depressive symptomatology was associated with decreased HRQoL

Table 1: Characteristics of Included Studies that Measures Health Related Quality of Life

Author (Publication Year)	Country	Study Design and Participants	Sample Size (n)	Average age year, M(SD)	% Women	Migraine Measures	Depression Measures	Anxiety Measures	HRQoL Measures	Main Findings
Lipton et al. (2000)[1]	US & UK	Cross- sectional population- based sample of subjects with migraine and nonmigraine controls	729		83%	ICHD-2	PRIME-MD		SF-12	Depression was associated with decrease in HRQoL (physical and mental health components)

BDI: Beck Depression Inventory; CESD: Center for Epidemiologic Studies-Depression Scale ;HADS: Hospital Anxiety and Depression Scale; HADS-A=Hospital Anxiety and Depression Scores - Anxiety Domain; HRQoL: Health-related Quality of life; ICHD-2: International Classification of Headache Disorders, second edition; ID Migraine: Three-item Identification of Migraine; MSQoL: Migraine-Specific Quality of Life; PHQ-9=9-item Patient Health ; PRIME-MD: Primary Care Evaluation of Mental Disorders, a mental health screening tool; Questionnaire; SF: Short Form Health Survey; WMH-CIDI: World Mental Health Composite International Diagnostic Interview Survey

Table 2: Characteristics of Included Studies that Measures Disability

Author (Publication Year)	Country	Study Design and Participants	Sample Size (n)	Average age year, M(SD)	% Women	Migraine Measures	Depression Measures	Anxiety Measures	Disability Measures	Main Findings
Seng et al. (2017)[25]	US	Cross-sectional study, subject with chronic migraine visiting tertiary headache center	90	45.0 (12.4)	85%	ICHD-2	PHQ	GAD-7	MIDAS	Higher depressive symptoms and anxiety symptoms were associated with severe migraine- related disability
McDermott et al. (2016) [27]		Cross-sectional study, subject admitted to a residential substance use disorder treatment program	153	36.4	37%	BHS	DASS	DASS	BHS	Depression and anxiety symptoms predict migraine- related disability
Dindo et al. (2015)[17]	US	Cross-sectional study, participants recruited for a clinical trial	93	32.0 (13.0)	89%	ID Migraine	Structured Clinical Interview for DSM- IV		WHO-DAS	Depression was negatively correlated to disability
Rossi et al. (2005)[28]	Italy	Cross-sectional study, subjects with episodic and chronic migraine visiting headache clinic	200	38.3 (10.7)	73%	ICHD-2	BDI		MIDAS	Depressive symptoms was a significant predictor of disability
Lanteri- Minet et al. (2005)[7]	France	Cross-sectional population-based study among adults with active migraine	1957	41.9 (14.5)	70%	ICHD-2	HADS	HADS	MIDAS	Comorbid anxiety and depression associated with migraine- related disability than either disease alone

Table 2: Characteristics of Included Studies that Measures Disability

Author (Publication Year)	Country	Study Design and Participants	Sample Size (n)	Average age year, M(SD)	% Women	Migraine Measures	Depression Measures	Anxiety Measures	Disability Measures	Main Findings
Breslau et al. (2003)[26]	USA	A cohort study of subjects with migraine	496	42.7 (8.2)	84%	ICHD-2	WHO CIDI		Headache Impact Questionnaire (HImQ)	Major depression was a significant predictor of migraine- related disability
Kolotylo et al. (2001)[24]		Cross-sectional mailed survey for women	247	43.4	100%	ICHD-2	CESD		The Henry Ford Hospital Disability Inventory	Depressive symptoms associated with disability.

BDI: Beck Depression Inventory; BHS: The Brief Headache Screen; CESD: Center for Epidemiologic Studies-Depression Scale ; DASS: Depression Anxiety Stress Scales—21 item; GAD-7: Generalized Anxiety Disorder-7; HADS: Hospital Anxiety and Depression Scale; ICHD-2: International Classification of Headache Disorders, second edition; ID Migraine: Three-item Identification of Migraine; MIDAS: migraine-related disability; MSQoL: Migraine-Specific Quality of Life; PHQ: The Patient Health Questionnaire; SF: Short Form Health Survey; WHO-DAS: World Health Organization Disability Assessment Schedule II; WHO CIDI: World Health Organization Composite International Diagnostic Interview

Table 3: Characteristics of Included Studies that Measures the Healthcare Costs and Utilization

Author (Publication Year)	Country	Study Design and Participants	Sample Size (n)	Average age year, M(SD)	% Women	Migraine Measures	Depression Measures	Anxiety Measures	Healthcare costs/utilization	Main Findings
Ford et al. (2019)[30]	US	Cross-sectional study, adults with migraine from 2008-2012 Medical Expenditures Panel Survey	1,735	39	79.8%	ICD-9-CM codes	ICD-9-CM codes	ICD-9-CM codes	Migraine-specific direct costs and non-migraine direct costs (outpatient, office visits, inpatient, and ER visits)	Comorbid anxiety and depression were associated with higher total and migraine-related health expenses.
Pesa j et al. (2004) [9]	US	Migraine cohorts were identified from one-year large employers database	11,332	41.4(9.8)	82%	ICD-9-CM codes or received a migraine medication	ICD-9-CM codes	ICD-9-CM codes	Healthcare costs from inpatient, outpatient, and prescription drug	Comorbid anxiety or depression was associated with significantly higher medical costs (outpatient, prescription drug, and total medical costs) than individuals with migraine alone
Wu et al. (2016)[29]	US	Cross-sectional study, adults with migraine from 2006-2012 Medical Expenditures Panel Survey	2,400		85%	ICD-9-CM codes	ICD-9-CM codes		Healthcare costs from inpatient, outpatient, and prescription drug ED visits	Comorbid depression was associated with higher total and migraine-related health expenses and increased likelihood of all-cause ED visits.

ICD-9-CM codes: International Classification of Diseases, Ninth Revision, Clinical Modification

Table 4 : Quality assessment of epidemiological studies included-Appraisal tool for Cross-Sectional Studies (AXIS)

Items	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
Prisnie JC	Y	Y	N	Y	Y	Y	N	Y	Y	Y	Y	Y	N	N	Y	Y	Y	Y	N	Y
Wang et al.	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	N	Y
D'Amico et al.	Y	Y	N	Y	Y	Y	N	Y	Y	Y	Y	Y	N	N	Y	Y	Y	Y	N	Y
Dindo et al.	Y	Y	N	Y	Y	Y	N	Y	Y	Y	Y	Y	N	N	Y	Y	Y	Y	N	Y
Kim et al.	Y	Y	N	Y	Y	Y	N	Y	Y	Y	Y	Y	N	N	Y	Y	Y	Y	N	Y
Sharma et al.	Y	Y	N	Y	Y	Y	N	Y	Y	Y	Y	Y	N	N	Y	Y	Y	Y	N	Y
Stuginski-Barbosa et al.	Y	Y	N	Y	Y	Y	N	Y	Y	Y	Y	Y	N	N	Y	Y	Y	Y	N	Y
Jette et al.	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	N	Y
Brna et al.	Y	Y	N	Y	Y	Y	N	Y	Y	Y	Y	Y	N	N	Y	Y	Y	Y	N	Y
Lanteri-Minet et al.	Y	Y	N	Y	Y	Y	N	Y	Y	Y	Y	Y	N	N	Y	Y	Y	Y	N	N
Kolotylo et al.	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	N	Y	Y	Y	Y	N	Y
Lipton et al.	Y	Y	N	Y	Y	Y	N	Y	Y	Y	Y	Y	N	N	Y	Y	Y	Y	N	Y
Fernández-de-las-Peña et al.	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	N	N	Y	Y	Y	Y	N	Y
Seng et al.	Y	Y	N	Y	Y	Y	N	Y	Y	Y	Y	Y	N	N	Y	Y	Y	Y	Y	N
McDermott et al.	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	N	Y	Y	Y	Y	N	Y
Rossi et al.	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	N	Y	Y	Y	Y	N	Y
Breslau et al.	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	N	Y	Y	Y	Y	N	N
Pesa et al.	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	N	Y	Y	Y	Y	N	N
Wu et al.	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	N	Y	Y	Y	Y	N	N
Fort et al.	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	N	Y	Y	Y	Y	N	N

Note: Y:Yes; N: No

- 1) Were the aims/objectives of the study clear?
- 2) Was the study design appropriate for the stated aim(s)?
- 3) Was the sample size justified?
- 4) Was the target/reference population clearly defined? (is it clear who the research was about?)
- 5) Was the sample frame taken from an appropriate population base so that it closely represented the target/reference population under investigation?
- 6) Was the selection process likely to select subjects/participants that were representative of the target/reference population under investigation?
- 7) Were measure undertaken to address and categorise non-responders?
- 8) Were the risk factor and outcome variables measured appropriate to the aims of the study?
- 9) Were the risk factor and outcome variables measured correctly using instruments/measurements that had been trialled, piloted or published previously?
- 10) Is it clear what was used to determine statistical significance and/or precision estimates? (e.g., p-values, confidence intervals)
- 11) Were the methods (including statistical methods) sufficiently described to enable them to be rejected?
- 12) Were the basic data adequately described?
- 13) Does the response rate raise concerns about non-response bias?
- 14) If appropriate, was information about non-responders described?
- 15) Were the results internally consistent?
- 16) Were the results presented for all the analyses described in the methods?
- 17) Were the authors' discussions and conclusions justified by the results?
- 18) Were the limitations of the study discussed?
- 19) Were there any funding sources or conflicts of interest that may affect the authors' interpretation of the results?
- 20) Was ethical approval or consent of participants attained?

Figures

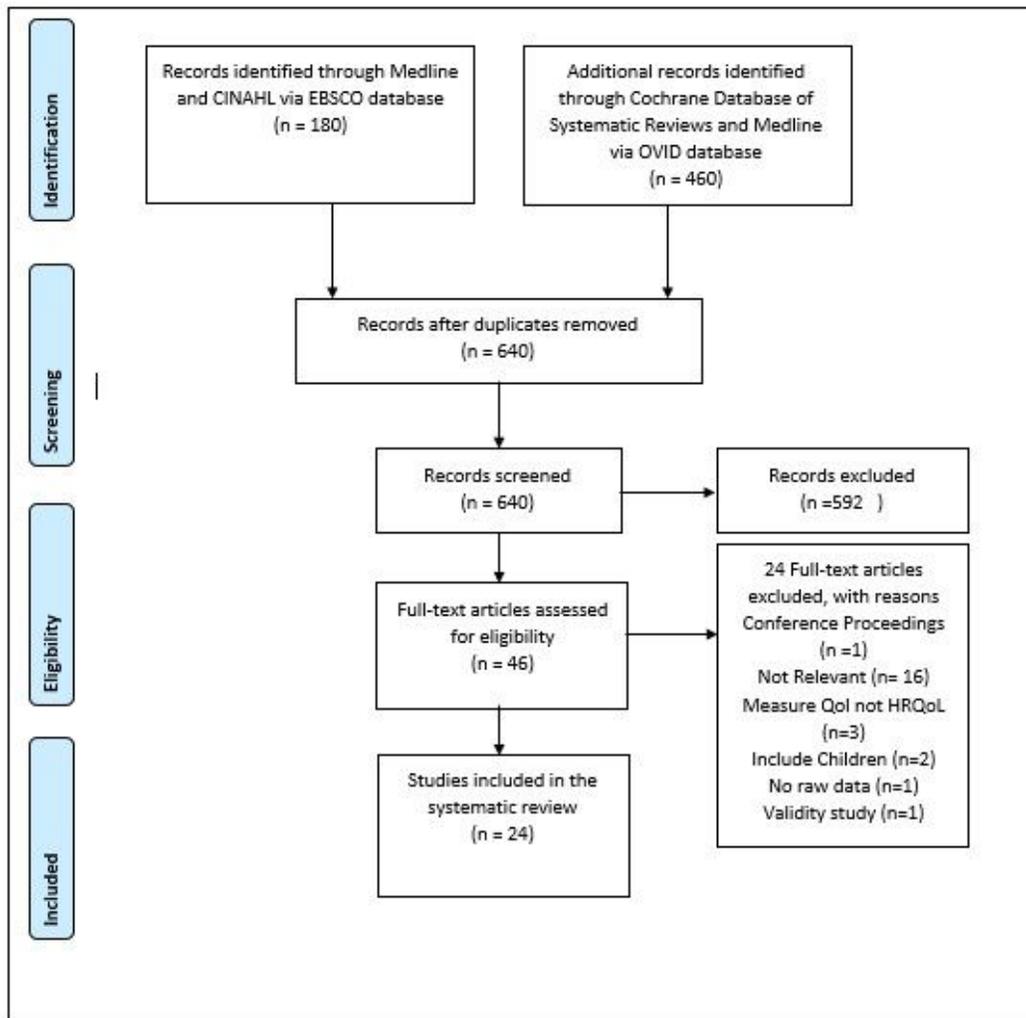


Figure 1

Identification and selection of articles for inclusion in this review

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [PRISMA2009checklistMigrainedepanxiety.doc](#)
- [APPENDIX.docx](#)