Title: Epidemiology of depression and anxiety in gout: A systematic review and meta-analysis

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ABSTRACT

Objective: To conduct a systematic review of depression and anxiety among patients with gout that specifically evaluates the prevalence, incidence, determinants, and impacts of these mental health comorbidities.

Methods: We conducted a literature search in Medline, Embase, Cochrane Database of Systematic Reviews, CINAHL, and PsycINFO using indexed terms and key words to identify studies reporting on depression/anxiety in patients with gout. This review included full-text articles published in English that reported on patients with gout, evaluated depression/anxiety using a routinely reported measure, and provided estimates or sufficient data on the prevalence, incidence, determinants, or impacts of depression/anxiety. Meta-analyses were conducted using random effects models.

Results: 20 of 901 articles identified through the search strategy met our inclusion criteria. All 20 studies evaluated depression, while only ten assessed anxiety (50.0%). Meta-analyses suggest a positive association between mental health disorders and gout, as resultant pooled odds ratios were 1.29 (95% confidence interval [CI] 1.07 to 1.56) for depression and 1.29 (95% CI 0.96 to 1.73) for anxiety. Findings from four studies reporting on the incidence of depression in patients with gout resulted in a pooled hazard ratio of 1.17 (95% CI 1.01 to 1.36). Significant determinants of depression included number of tophi, frequency of flares, and oligo/polyarticular gout.

Conclusions: Our systematic review suggests depression and anxiety are significantly associated with gout and highlights the need for future research to focus on the onset of mental disorders after gout diagnosis as well as identify potential targets for intervention.

INTRODUCTION

Substantial increases in the prevalence of gout has been observed in multiple countries (1-4) and specifically one longitudinal study in the UK reported a 64% increase in prevalence from 1997 to 2012 (1). Although gout can be effectively treated with urate lowering therapy (ULT), the management of gout is consistently suboptimal as evidenced by one Canadian study showing that less than one-quarter of patients received ULT between 2000 and 2012 (2) and among those prescribed, evidence suggests that only 10-46% of patients are adherent to ULT (5). Additional challenges to the management of gout are the several comorbidities associated with this chronic disease (6). Comorbidity management in gout primarily focuses on diseases such as type II diabetes, chronic kidney/renal disease, hypertension, and hyperlipidemia (7, 8) and the literature often highlights the increased burden of other physical comorbidities such as cardiovascular disease in this patient population (9-11). However, as with other types of rheumatic diseases, such as rheumatoid arthritis (RA) (12) and systemic lupus erythematosus (13), depression and anxiety are common yet underrecognized comorbidities among individuals with gout. Indeed, a study from the UK suggests the risk of incident depression (hazard ratio [HR] 1.19, 95% confidence interval [CI] 1.12, 1.26) among newly diagnosed cases of gout is similar to the risk of myocardial infarction (HR 1.16, 95% CI 1.05 to 1.28) (10). As mental disorders can introduce or exasperate challenges related to chronic disease management, such as disease activity (14, 15) and medication adherence (16, 17), it is important to understand how mental illness affects patients with gout.

To date, one systematic review identified seven articles on the association of depression and gout and reported a pooled odds ratio (OR) of 1.19 (95% CI 1.11 to 1.29) (18). However, a comprehensive synthesis that distinguishes depression prevalence from incidence in individuals with gout, as well as examines its determinants, is warranted. Moreover, anxiety, which is characterized by excessive and continuous worry and is associated with quality of life impairment (19), is another

common mental disorder among persons with rheumatic disease that requires further evaluation (13). As such, to provide a thorough understanding of mental disorders among persons with gout, our objective was to systematically review literature examining the prevalence, incidence, determinants, and impacts of depression and anxiety in individuals with gout.

MATERIALS AND METHODS

Literature Search Strategy

We developed a search strategy with a research librarian who then searched five health-related databases in November 2019. The databases searched were Medline (1946-), Embase (1974-), Cochrane Database of Systematic Reviews (2005-) on the Ovid platform, CINAHL Complete (1982-), and PsycINFO (1880-) on Ebscohost. The search strategy included both subject headings for topics that were well-indexed as well as key words to optimize the search results (**Supplementary Material 1**). To supplement the database searches, we conducted a hand search of bibliographies of included papers.

Study Selection

After the removal of duplicates, we reviewed titles, abstracts, and full-texts of manuscripts identified in the search using the following criteria: 1) full-text observational study published in a peer-reviewed journal; 2) study sample of patients with gout; 3) anxiety and/or depression evaluated as an outcome variable, explanatory variable, or comorbidity; 4) anxiety and/or depression evaluated using a routinely reported measures (e.g., International Classification of Diseases [ICD] codes, validated questionnaires such as Patient Health Questionnaire 9-item [PHQ-9]); 5) availability of estimates measuring prevalence (e.g., proportion) or incidence (e.g., hazard ratio [HR]) of depression and/or anxiety, or sufficient data to allow calculation; and 6) published in English. Conference

abstracts and grey literature were not included in this systematic review. Two study authors participated in study selection (AH, MDV) and discrepancies were resolved by discussion.

Data Extraction and Quality Assessment

General characteristics that we extracted from included articles were: country, year of publication, study design, sample size, age of sample, gender, and method of gout diagnosis. For this review, we specifically focused on extracting data describing the prevalence and/or incidence of depression/anxiety (e.g., prevalence as a proportion (%) and/or OR) as well as the measures applied to assess depression/anxiety (e.g., PHQ-9). Finally, our review included data from studies that used multivariable analyses to assess factors independently associated with depression/anxiety and also the effect of depression/anxiety on patient outcomes (e.g., quality of life).

Two study authors (AH and DB) evaluated the quality of included articles using the Newcastle – Ottawa Scale (NOS) for quality assessment of case-control and cohort studies (20). Articles that used a cross-sectional study design were assessed using a modified version of the NOS that had been adapted for cross-sectional studies (21). We introduced minor adjustments to the NOS, and these included having a maximum of one star for 'comparability' to thereby reduce the overall maximum quality score to eight for cohort studies and nine for cross-sectional studies. Specifically, articles would receive one star if the methodology applied a multivariable analysis or included a comparator group matched on specified confounding variables. All of our assessments considered 'gout' as the exposure variable and 'depression' and/or 'anxiety' as the outcome variable. Both authors first independently assessed and scored all of the included articles. During the collective quality review, if quality assessment scores differed for articles, authors reviewed study characteristics until a final consensus score was determined.

Statistical Analysis

Estimates from included studies that reported the odds or risk for depression and anxiety in individuals with gout were meta-analysed using random-effect models (DerSimonian and Laird), with heterogeneity assessed using I-squared values. The meta-analyses included calculated unadjusted odds ratios for those studies that included a comparator group but did not conduct a multivariable analysis. We selected one estimate from the most recent publication when studies reported on data from the same population sample (22, 23). We assessed the potential for publication bias using funnel plots. Statistical analyses were done using Stata V.14 (StataCorp, College Station, TX, USA).

RESULTS

Literature Search

Our literature search across five databases returned a total of 901 articles, and after the removal of duplicates 784 articles remained for title and abstract review (**Figure 1**). We reviewed the full-text manuscripts of 34 articles, and ultimately 20 articles were included in this review. Characteristics of the included studies are presented in **Table 1**. Studies were predominately cross-sectional (n= 12, 60.0%) and eight were cohort studies (40.0%). The majority of studies identified patients with gout using billing codes from administrative health databases (i.e., Read codes or ICD codes) (n= 10, 50.0%) or using diagnostic criteria from the American College of Rheumatology (n= 7, 35.0%). Quality assessment scores of included studies ranged from 5 to 8 and the average score was 7.3 (± 0.5) for cohort studies and 6.6 (±0.8) for cross-sectional studies.

Prevalence and Incidence of Depression

Nineteen studies assessed the prevalence or incidence of depression among patients with gout using administrative billing codes (n= 8, 40.0%) (10, 24-30), validated screening questionnaires or interviews (n= 10, 50.0%) (22, 23, 31-38), or as a self-reported physician diagnosis (n= 1, 5.0%) (39). Studies varied according to the type of screening questionnaire applied to measure depression and those specifically used were: PHQ-9 (n=5) (22, 23, 32, 35, 37); Hospital Anxiety and Depression Scale - Depression (HADS-D) (n=2) (31, 34); Center for Epidemiological Studies Depression Scale (CES-D) (n=1) (33); Geriatric Depression Scale (Short Form) (n=1) (36); and the 17-item Hamilton Depression Scale followed by structured clinical interview (n=1) (38). Reported prevalence proportions for depression in patients with gout, as reported by 12 studies(22, 23, 25, 26, 28, 30, 33-35, 37-39), ranged from 1.9% to 40%. Prevalence estimates were lowest (1.9% and 2.6%) in the two studies conducted using administrative health data from Taiwan, specifically the National Health Insurance Research Database (NHIRD) (25, 26). In contrast, higher prevalence estimates were presented in studies measuring depression using the PHQ-9 (13% to 17%) (22, 23, 35, 37), structured clinical interview using the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (17.2%) (38), HADS-D (20%) (34), and self-report (23%) (39), with the highest estimate reported by a study employing the CES-D (40%) (33).

A total of ten studies that evaluated the prevalence of depression included a comparator group comprised of individuals without a gout diagnosis (22, 23, 25, 26, 30-32, 34, 36, 39). Two of these studies sampled participants from Taiwan's NHIRD (25, 26) using overlapping time periods and therefore the article reporting on the widest time interval by Hsu et al. (26) was selected for meta-analysis. Our meta-analysis, based on more than 38,009 patients with gout (an approximation as one study (32) did not provide the sample size for their gout population), resulted in a pooled OR of 1.29 (95% CI 1.07 to 1.56) (**Figure 2a**). Four studies evaluated the incidence of depression among patients with gout using administrative billing codes to define depression (10, 24, 27, 29)and

findings from our meta-analysis (>n= 74,850 gout, >n= 113,967 without gout; estimates as one study (29) did not specify sample sizes) yielded a pooled HR of 1.17 (95% CI 1.01 to 1.36) (**Figure 2b**). Evaluation of the funnel plot (**Supplementary Material 2, Figure 1b**) pertaining to HR estimates of depression suggests evidence of publication bias.

Prevalence and Incidence of Anxiety

As compared to depression, anxiety was less often evaluated among patients with gout, with only nine studies reporting on the prevalence or incidence of anxiety (22, 23, 26, 27, 30, 31, 34, 35, 37). The prevalence of anxiety was most often assessed using the Generalized Anxiety Disorder 7-item (n=4) (22, 23, 35, 37), followed by the Hospital Anxiety and Depression Scale – Anxiety (n=2) (31, 34), and using administrative billing codes (n=2) (27, 30). In addition to its infrequent assessment, the overall burden of anxiety in patients with gout appeared lower compared to depression, with prevalence estimates ranging from 3.8% to 10.0%. Pooling ORs from five studies (22, 26, 30, 31, 34) (n = 36,682 with gout, n = 82,734 without gout) resulted in a OR of 1.29 (95% CI 0.96 to 1.73). Pooled estimates from the meta-analysis are shown in **Figure 3**. Only one study using administrative health data estimated the risk of anxiety among patients with gout and reported an adjusted HR of 1.01 (95% CI 0.87 to 1.16) (27).

Determinants of Depression and Anxiety

Factors that were assessed as independent determinants of depression and anxiety are listed in **Table 2** and include gout-specific factors, clinical characteristics such as disability and health-related quality of life (HRQOL), as well as sociodemographic characteristics. Indeed, Prior et al.'s (35) analysis suggests that oligo/polyarticular gout is positively associated with depression (OR 2.01, 95% CI 1.2 to 3.3). Stratification by allopurinol use increased estimates pertaining to

oligo/polyarticular gout and also indicated that patients with gout on allopurinol who reported ≥3 gout attacks in the previous 12 months had higher odds of experiencing symptoms of depression, as compared to patients without gout attacks (OR 2.87, 95% CI 1.2 to 6.6) (35). Zhou et al. (38) similarly reported that frequency of gout attacks and attacks occurring in multiple joints were associated with increased odds for depression. Additional factors related to gout severity, specifically, number of tophi and physical disability, were also associated with increased odds for depression (22). One of the factors associated with reduced odds for depression symptoms was better quality of life as measured by the mental health component of the Short Form 36 Health Survey (SF-36) (22). A cohort study by Changchien et al. (24) further showed that patients with gout taking antigout medications (e.g., colchicine, ULTs) had a lower risk of depression. While several gout-specific factors did not have a significant association with anxiety (35), it was noted by Fu et al. (22) that higher education and better SF-36 mental health scores were associated with a decreased odds for symptoms of anxiety.

Impacts of Depression and Anxiety

Six studies, using cross-sectional (n=3) (23, 37, 40) and cohort (n=3) (25, 26, 28) study designs, evaluated the association of depression and anxiety with patient outcomes and significant findings are presented in **Table 3**. Two of the cross-sectional studies observed that depression and anxiety have significant associations with quality of life for patients living with gout, specifically reporting a lower HRQOL and higher functional limitations when compared to patients with gout without depression or anxiety (23, 40). Lastly, a 2015 cohort study that included 35,265 men with gout by Hsu et al. (26) found that both depression and anxiety in the context of gout were associated with an increased risk for erectile dysfunction.

DISCUSSION

From our systematic review that included 20 articles describing the burden, risk, determinants, and impacts of depression and anxiety for patients with gout, we found that individuals with gout have 29% increased odds for presenting with symptoms of depression and while non-significant, a29% increased odds for having symptoms of anxiety. Although there are fewer studies reporting on the risk of incident depression and anxiety following a gout diagnosis, our resultant meta-analyses suggest a 17% increased hazard for depression. Importantly, several determinants of depression and anxiety in patients with gout were identified, which include oligo/polyarticular gout and number of tophi for depression as well as quality of life and education for anxiety (22, 35). Overall, findings from our synthesis emphasize that patients with gout have an elevated burden of mental disorders and as such, depression and anxiety should also be monitored when managing patients with gout.

Prior to our systematic review, Lin et al. (18) published a systematic review that meta-analyzed various point estimates (e.g., OR and HR) from seven studies, and their findings indicated a positive association between gout and depression with a resultant OR of 1.19 (95% CI 1.11 to 1.29). We have added to the present literature by expanding our review to include anxiety as well as more than doubling the total number of articles included. Further, in an effort to clarify the odds and risk of depression and anxiety among patients with gout as compared to controls, we conducted distinct meta-analyses according to the study design and hence, the reported point estimate. Our results suggest that patients with gout have increased odds to experience symptoms affecting their mental health, with equivalent pooled ORs for depression (OR 1.29, 95% CI 1.07 to 1.56) and anxiety (OR 1.29, 95% CI 0.96 to 1.73), although the confidence interval for the latter estimate did not reach significance. In addition, estimates pertaining to the prevalence proportion for depression and

anxiety among patients with gout ranged from 1.9% to 40% and 3.8% to 10.0%, respectively. These wide prevalence estimates are potentially related to the diverse study populations, data sources, and various methods (e.g., ICD codes, PHQ-9) used to identify symptoms of depression and anxiety. In comparison to RA where the pooled prevalence of depression based on 659 patients with RA according to the PHQ-9 is 38.8% (95% CI 34.0% to 43.0%) (12), individuals with gout appear to have a lower burden of depression as per the PHQ-9 where prevalence has been reported as high as 17% (37). While both RA and gout are associated with an increased burden of depression and anxiety, psychological interventions to date have been heavily focused on patients with RA (41, 42), and therefore future research efforts should also be addressing mental health for the gout patient population.

To further characterize the epidemiology of depression and anxiety in patients with gout, we also synthesized studies that evaluated the risk of mental disorders after a diagnosis of gout. A total of four articles identified from our search published adjusted estimates describing the risk of depression in patients with gout that when meta-analysed indicated a 17% increased risk for incident depression (HR 1.17, 95% CI 1.01 to 1.36). Interestingly, Kuo et al. (10) found that as with other comorbidities, the cumulative probability of incident depression increases over time in comparison to matched controls, specifically doubling over a ten year period from the time of diagnosis for patients with gout. The most recent cohort study measuring incident depression included in our review by Singh et al. (29) in 2018 that was based on a US Medicare sample (≥ 65 years of age) reported a 42% increased risk (HR 1.42, 95% CI 1.38 to 1.45) for incident depression among patients with gout as compared to matched controls. Assessment of covariates from the multivariable analysis for this study also suggested that women have an 80% increased risk for incident depression as compared to men (29). These findings are also supported by a 2015 cross-

sectional study conducted in the UK, where the association between depression and gout, when stratified by sex, was significant for females (OR 5.00, 95% CI 1.26 to 19.82) but was non-significant for males (OR 1.43, 95% CI 0.57 to 3.55) (32). Though gout predominately affects men compared to women (3, 43), the observation of more women experiencing depressive symptoms in the context of gout is reflective of current literature for the general population showing up to two times more women than men experience mental disorders such as depression and anxiety (44, 45). When interpreting differences between men and women it is also important to consider differences in health-seeking behaviour for mental health, with evidence depicting a tendency for women to seek mental health care and men to be under-treated (46, 47). Finally, even though anxiety is one of the most common mental disorders, affecting approximately 3.6% of the global population (48), our review retrieved only one article from the UK that showed no significant risk for incident anxiety in patients with gout (27). Therefore, recommendations from our synthesis include further characterizing the incidence of mental disorders in patients with gout, given the heterogeneity between depression risk estimates published thus far and the lack of published data describing anxiety, as well as further evaluating the impact of sex and gender.

Beyond quantifying the burden and risk of mental disorders, it was also imperative to identify factors that are independent determinants of depression and anxiety to inform practical recommendations. Relevant to clinical practice, were several modifiable risk factors associated with depression that can be addressed through improving quality of care for gout, which is persistently suboptimal (49-52). Studies consistently report insufficient prescribing and monitoring of anti-gout medications (50, 52), highlight low adherence to ULT (5), and consequently note an insufficient proportion of patients reaching targeting serum urate (SUA) levels (51, 52). These high levels of SUA can increase gout disease severity, specifically increasing gout flares, number of tophi, and

oligo/polyarticular gout, all of which are associated with depression (22, 35). Our systematic review also identified one cohort study that showed taking anti-gout medications (i.e., colchicine, uricosuric agents, xanthine oxidase inhibitors) is associated with a 30% decreased risk of incident depression (24). Therefore, improving quality of care for gout extends beyond addressing disease severity and treatment adherence, but is also closely integrated with impacting mental health comorbidities for patients with gout.

Our systematic review describing the epidemiology of depression and anxiety in patients with gout identified articles using search strategies developed with a research librarian and utilized five international reference databases. An additional strength of our review was that data extraction and meta-analyses focused on distinguishing study design and point estimates to describe both the prevalence as well as incidence of depression and anxiety in patients with gout. Limitations to our study include the potential for publication bias as our inclusion criteria were restricted to peer-reviewed full-text publications. This review focused on the epidemiology of depression and anxiety as these mental disorders are most frequently studied; however, a complete understanding of mental health comorbidities in patients with gout could also expand to include other conditions known to be associated with rheumatic diseases, such as bipolar disorder (53).

As demonstrated in our systematic review, patients with gout experience an increased likelihood to have comorbid depression and anxiety as compared to controls, and the severity of several gout characteristics are associated with the presence of mental health disorders in this population. Opportunities to better comprehend the mental health burden in patients with gout include conducting longitudinal cohort studies to evaluate the risk of depression and anxiety after gout diagnosis as well as broadening our knowledge on determinants, such as sociodemographic

characteristics, to inform clinical monitoring for depression and anxiety. As mental disorders may go unnoticed in the rheumatology setting (54), our findings have implications for clinical practice as health care providers (including rheumatologists, general practitioners, nurses, and pharmacists who routinely interact with gout patients) should be aware of the heightened burden of depression and anxiety when treating patients diagnosed with gout.

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FIGURE LEGENDS

Figure 1. Flow diagram of search results for systematic review.

Figure 2. Pooled odds ratio (OR) **(A)** and pooled hazard ratio (HR) **(B)** for depression in patients with gout.
Abbreviations: CI – confidence interval

Figure 3. Pooled odds ratio (OR) for anxiety in patients with gout.
Abbreviations: CI – confidence interval

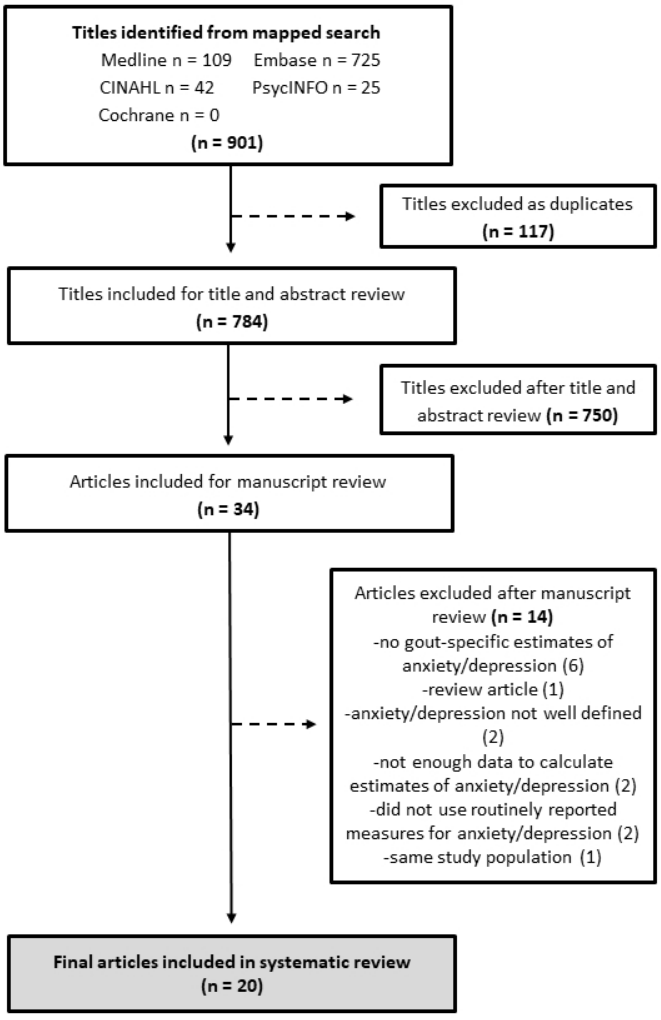

Figure 1. Flow diagram of search results for systematic review.

190x254mm (96 x 96 DPI)

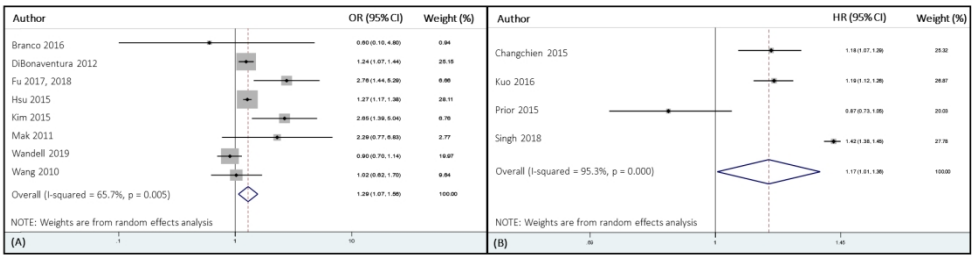

Figure 2. Pooled odds ratio (OR) (A) and pooled hazard ratio (HR) (B) for depression in patients with gout.
Abbreviations: CI – confidence interval

508x152mm (96 x 96 DPI)

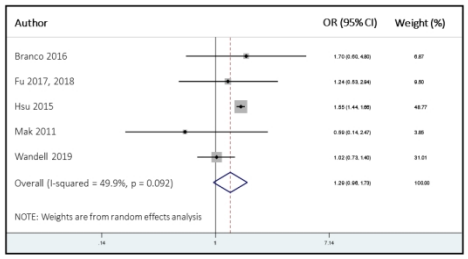

Figure 3. Pooled odds ratio (OR) for anxiety in patients with gout.
Abbreviations: CI – confidence interval

508x152mm (96 x 96 DPI)

Table 1. Characteristics of included studies

Author, year	Country	Study Design	Population/ Setting/Data Source	Sample Size	Age (years), mean (standard deviation)	Gender (% males)	Gout assessment	Quality assessment[e]
Kobayashi-Gutierrez 2009	Mexico	cross-sectional (no comparator)	outpatient (rheumatology)	all: 145[a] gout: 5	all: 46 ± 16.1	all: 13.9	ACR criteria	7
Wang 2010	Taiwan	cross-sectional (w comparator)	survey	gout: 305 no gout: 3,665	NR	gout: 67.9 no gout: 54.8	self-report	5
Mak 2011	Singapore	cross-sectional (w comparator)	outpatient (rheumatology)	gout: 50 no gout: 61	gout: 58.2 ± 14.9 no gout: 42.8 ± 14.0	gout: 90.0 no gout: 13.1	ACR criteria	7
DiBonaventura, 2012	USA	cross-sectional (w comparator)	survey (respondents with HTN)	HTN gout: 1,022 HTN no gout: 21,664	HTN gout: 61.4 ± 11.8 HTN no gout: 58.1 ± 13.7	HTN gout: 75.5 HTN no gout: 52.5	self-reported physician diagnosis	5
Changchien 2015	Taiwan	cohort	administrative health database	gout: 34,050 no gout: 68,100	gout: 49.3 ± 16.0 no gout: 48.8 ± 16.2	gout: 80.2 no gout: 80.2	ICD-9	8
Chen 2015	Taiwan	cohort	administrative health database	gout: 19,368 no gout: 77,472	gout: 42.7 ± 12 no gout: 42.7 ± 12	gout: 100 no gout: 100	ICD-9	7
Hsu 2015	Taiwan	cohort	administrative health database	gout: 35,265 no gout: 70,529	gout: 49.6 ± 16.2 no gout: 49.1 ± 16.5	gout: 100 no gout: 100	ICD-9	
Kim 2015	USA	cross-sectional (w comparator)	survey	all[b]: 2,266	NR	all: 43.5	self-report	
Prior 2015	UK	cohort	outpatient (primary care)	gout: 1,689 no gout: 6,756	gout: 63 ± 16 no gout: NR	gout: 76 no gout: NR	Read code	9
Branco 2016	Portugal	cross-sectional (w comparator)	survey	gout: 92 no RMD: 678	NR	NR	ACR criteria	
Kuo 2016	UK	cohort	administrative health database	gout: 39,111 no gout: 39,111	gout: 62.2 ± 15.1	gout: 72.5 no gout: 72.5	Read code	
Prior 2016	UK	cross-sectional (no comparator)	administrative health database & survey	gout: 1,184	65.6 ± 12.5	81.5	Read code	
Fu 2017[c] Fu 2018[c]	China	cross-sectional (w comparator)	hospital inpatients and outpatients	gout: 226 no gout: 232	gout: 53.2 ± 15.8 no gout: 51.2 ± 13.5	gout: 94.7 no gout: 94	ACR criteria	
Yin 2017	China	cross-sectional (no comparator)	hospital inpatients and outpatients	125	55.2 ± 14.9	94	ACR criteria	
Chandratre 2018	UK	cross-sectional (no comparator)	outpatient (primary care)	1,184	65.6 ± 12.5	83.6	Read code	

Scheepers 2018	UK	cohort	administrative health database	48,280	64.6 ± 13.2	75.7	Read code + allopurinol prescription	7
Singh 2018	USA	cohort	administrative health database	all[d]: 1,693,515	all[d]: 75.3 ± 7.6	all[d]: 42.9	ICD-9	7
Wandell 2019	Sweden	cohort	administrative health database	AF gout: 1,049 AF no gout: 11,234	AF gout (male): 73.5 ± 9.3 AF gout (female): 78.4 ± 8.1 AF no gout (male): 72.0 ± 10.2 AF no gout (female): 77.0 ± 93.3	AF gout: 65.5 AF no gout: 53.0	ICD-10	7
Zhou 2019	China	cross-sectional (no comparator)	survey	186	61.9 ± 10.9	81.2	ACR criteria	7

[a]All refers to entire study sample with rheumatic diseases (e.g., gout, rheumatoid arthritis etc.).
[b]All refers to every individual from the general population that completed the study survey.
[c]Two separate studies using same patient sample but both are included in the review as one evaluated anxiety/depression as determinant of a patient outcome (2017) and one evaluated determinants of anxiety/depression (2018).
[d]All refers to the entire study cohort
[e]The maximum quality assessment score was eight for cohort and nine for cross-sectional studies.
Abbreviations: ACR – American College of Rheumatology; AF – Atrial Fibrillation; ICD-9: International Classification of Diseases 9th Revision Code; HTN – hypertension; NR – not reported; RMD – rheumatic disease

Table 2. Factors assessed for independent associations with depression and anxiety among patients with gout as identified using multivariable analyses

Factor	Depression Estimate (95% confidence interval)	Anxiety Estimate (95% confidence interval)
Gout-specific factors		
Frequency of gout attacks (Prior 2016)		
1-2 gout attacks (reference = 0)	on allopurinol (a)OR: 1.49 (0.70 to 3.40)	on allopurinol (a)OR: 0.76 (0.30 to 1.80)
	no allopurinol (a)OR: 0.64 (0.20 to 1.90)	no allopurinol (a)OR: 0.57 (0.20 to 1.80)
≥3 gout attacks (reference = 0)	**on allopurinol (a)OR: 2.87 (1.2 to 6.6)**	on allopurinol (a)OR: 1.72 (0.7 to 4.3)
	no allopurinol (a)OR: 1.16 (0.3 to 4.1)	no allopurinol (a)OR: 2.07 (0.6 to 7.4)
Oligo/polyarticular gout (Prior 2016)	**on allopurinol (a)OR: 2.09 (1.1 to 4.0)**	on allopurinol (a)OR: 0.94 (0.5 to 1.9)
(reference= no oligo/polyarticular gout)	**no allopurinol (a)OR: 2.64 (1.0 to 6.8)**	no allopurinol (a)OR: 1.04 (0.4 to 3.0)
Gout duration (Prior 2016)		
3-8 years (reference = ≤2 years)	on allopurinol (a)OR: 1.27 (0.40 to 3.80)	on allopurinol (a)OR: 0.96 (0.30 to 3.30)
	no allopurinol (a)OR: 0.46 (0.20 to 1.30)	no allopurinol (a)OR: 0.57 (0.20 to 1.60)
9-17 years (reference = ≤2 years)	on allopurinol (a)OR: 2.11 (0.70 to 6.40)	on allopurinol (a)OR: 1.90 (0.60 to 6.30)
	no allopurinol (a)OR: 0.45 (0.10 1.70)	no allopurinol (a)OR: 0.34 (0.10 to 1.40)
≥ 18 years (reference = ≤2 years)	on allopurinol (a)OR: 2.11 (0.7 to 6.3)	on allopurinol (a)OR: 2.99 (0.9 to 9.8)
	no allopurinol (a)OR: 0.92 (0.3 to 3.2)	no allopurinol (a)OR: 0.77 (0.2 to 3.1)
Number of tophi (Fu 2018)	**(a)OR: 1.74 (1.05 to 2.90)**	
Antigout medication (Changchien 2015)	**(a)HR: 0.70 (0.55 to 0.88)**	
Frequent gout attacks (≥3) (Zhou 2019)	**(a)OR: 6.14 (1.74 to 21.67)**	
Gout attacks in multiple joints (Zhou 2019)	**(a)OR: 4.45 (1.45 to 13.51)**	
Clinical characteristics		
Disability (HAQ-DI) (Fu 2018)	**(a)OR: 3.62 (1.61 to 8.18)**	
HRQOL (SF-36, MCS) (Fu 2018)	**(a)OR: 0.94 (0.91 to 0.98)**	**(a)OR: 0.87 (0.80 to 0.94)**
25-hydroxyvitamin D (≤40.0 nmol/L) (Zhou 2019)	**(a)OR: 3.83 (1.41 to 10.45)**	
Sociodemographic characteristics		
Education (Fu 2018)		**(a)OR: 0.16 (0.03 to 0.86)**
Age (Zhou 2019)	(a)OR: 0.99 (0.95 to 1.03)	
Sex (Zhou 2019)	(a)OR: 1.01 (0.32 to 3.18)	

Abbreviations: (a)HR – adjusted hazard ratio; (a)OR – adjusted odds ratio; HAQ-DI – Health Assessment Questionnaire-Disability Index; HRQOL – Health-related Quality of Life; SF-36-MCS - Short Form 36 Health Survey, Mental Components Summary;
Values in bold were significantly associated with depression or anxiety.

Table 3. Outcomes significantly impacted by depression and anxiety among patients with gout as identified using multivariable analyses

Outcome	Depression	Anxiety
HRQOL		
SF-36 MCS (Fu 2017)	β: -14.27 (-22.09 to -6.45)	β: -13.45 (-25.48 to -1.43)
SF-36 PCS (Fu 2017)	β: -16.65 (-23.93 to -9.37)	
SF-36 PCS (Chandratre 2018)	β: -1.98 (-2.24 to -1.71)	β: -1.81 (-2.14 to -1.47)
GIS CO (Chandratre 2018)	β: 0.84 (0.50 to 1.19)	β: 0.88 (0.50 to 1.26)
GIS MSE (Chandratre 2018)	β: 1.07 (0.72 to 1.42)	β: 1.11 (0.72 to 1.50)
GIS UTN (Chandratre 2018)	β: 0.42 (0.16 to 0.69)	β: 0.38 (0.08 to 0.68)
GIS WBDA (Chandratre 2018)	β: 1.47 (1.13 to 1.82)	β: 1.44 (1.05 to 1.82)
GIS CDA (Chandratre 2018)	β: 1.47 (1.16 to 1.78)	β: 1.70 (1.36 to 2.05)
Disability		
HAQ-DI (Fu 2017)	β: 2.11 (3.57 to 19.23)	
HAQ-DI (Chandratre 2018)	β: 0.06 (0.05 to 0.07)	β: 0.06 (0.05 to 0.07)
Comorbidities		
Erectile dysfunction (Hsu 2015)	(a)HR: 2.01 (1.53, 2.65)	(a)HR: 1.50 (1.15, 1.97)

Abbreviations: (a)HR – adjusted hazard ratio; GIS – Gout Impact Scale [CDA – concern during attack; CO – concern overall; MSE – medication side effects; UTN – unmet treatment need; WBDA – wellbeing during attack]; HAQ-DI – Health Assessment Questionnaire – Disability Index; HRQOL – health-related quality of life; SF-36 MCS – 36-Item Short Form Survey Mental Component Score; SF-36 PCS – 36-Item Short Form Survey Physical Component Score.