

# Epidemiology of Depression and Anxiety in Gout: A Systematic Review and Metaanalysis

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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 effects 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 effects of depression/anxiety. Metaanalyses were conducted using random effects models.

**Results.** Twenty of 901 articles identified through the search strategy met our inclusion criteria. All 20 studies evaluated depression, while only 10 assessed anxiety (50%). Metaanalyses suggest a positive association between mental health disorders and gout, as resultant pooled OR were 1.29 (95% CI 1.07–1.56) for depression and 1.29 (95% CI 0.96–1.73) for anxiety. Findings from four studies reporting on the incidence of depression in patients with gout resulted in a pooled HR of 1.17 (95% CI 1.01–1.36). Significant determinants of depression included number of tophi, frequency of flares, and oligo/polyarticular gout.

**Conclusion.** Our systematic review suggests that depression and anxiety are significantly associated with gout, highlighting the need for future research to focus on the onset of mental disorders after gout diagnosis. We also identify potential targets for intervention.

*Key Indexing Terms:* anxiety, depression, gout, mental disorders, metaanalysis, systematic review

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Substantial increases in the prevalence of gout have been observed in multiple countries<sup>1,2,3,4</sup>, with 1 longitudinal study in the UK reporting a 64% increase in prevalence from 1997 to 2012<sup>1</sup>. Although gout can be effectively treated with urate-lowering therapy (ULT), the management of gout is consistently suboptimal, as evidenced by 1 Canadian study showing that less than one-quarter of patients received ULT between 2000 and 2012<sup>2</sup>. Among those treated, evidence suggests that only 10–46% of patients are adherent to ULT<sup>5</sup>. Additional challenges to the management of gout are the several comorbidities associated with this chronic disease<sup>6</sup>. Comorbidity management in gout primarily focuses on diseases such as type 2 diabetes, chronic kidney/renal disease, hypertension, and hyperlipidemia<sup>7,8</sup>, and the literature often highlights the increased burden of other physical comorbidities, such as cardiovascular disease in the patient population<sup>9,10,11</sup>. However, as with other types of rheumatic diseases like rheumatoid arthritis (RA)<sup>12</sup> and systemic lupus erythematosus<sup>13</sup>, depression and anxiety are common yet underrecognized comorbidities among individuals with gout. Indeed, a study from the UK suggests the risk of incident depression (HR 1.19, 95% CI 1.12–1.26) among newly diagnosed cases of gout is similar to the risk of myocardial infarction (HR 1.16, 95% CI 1.05–1.28)<sup>10</sup>. As mental disorders can introduce or exacerbate challenges related to chronic disease management, such as

disease activity<sup>14,15</sup> and medication adherence<sup>16,17</sup>, it is important to understand how mental illness affects patients with gout.

To date, 1 systematic review identified 7 articles on the association of depression and gout and reported a pooled OR of 1.19 (95% CI 1.11–1.29)<sup>18</sup>. 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 (QOL) impairment<sup>19</sup>, is another common mental disorder among persons with rheumatic diseases that requires further evaluation<sup>13</sup>. 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 effects 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 5 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 Table 1, available with the online version of this article). 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 the 9-item Patient Health Questionnaire (PHQ-9)]; (5) availability of estimates measuring prevalence (e.g., proportion) or incidence (e.g., 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 as follows: country, year of publication, study design, sample size, age of sample, sex, 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., QOL).

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<sup>20</sup>. 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<sup>21</sup>. We introduced minor adjustments to the NOS, which included having a maximum of 1 star for “comparability” to thereby reduce the overall maximum quality score to 8 for cohort studies and 9 for cross-sectional studies. Specifically, articles would receive 1 star if the methodology applied a multivariable analysis or included a comparator

group matched on specified confounding variables. All 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 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 of depression or anxiety in individuals with gout were metaanalyzed using random-effect models (DerSimonian and Laird), with heterogeneity assessed using  $I^2$  values. The metaanalyses included calculated unadjusted OR for those studies that included a comparator group but did not conduct a multivariable analysis. We selected 1 estimate from the most recent publication when studies reported on data from the same population sample<sup>22,23</sup>. We assessed the potential for publication bias using funnel plots. Statistical analyses were done using Stata V.14 (StataCorp.).

## RESULTS

**Literature search.** Our literature search across 5 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 predominantly cross-sectional ( $n = 12$ , 60%); 8 were cohort studies (40%). The majority of studies identified patients with

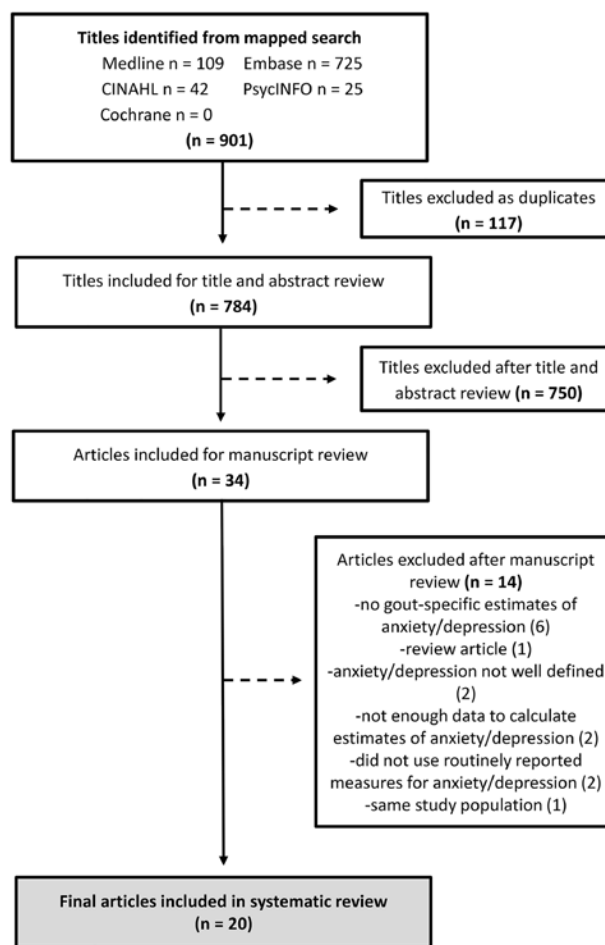


Figure 1. Flow diagram of search results for systematic review.

Table 1. Characteristics of included studies.

Author, Yr	Country	Study Design	Population/ Setting/ Data Source	Sample Size	Age (yrs), Mean (SD)	Sex (% males)	Gout Assessment	Quality Assessment <sup>e</sup>
Kobayashi-Gutierrez, 2009 <sup>33</sup>	Mexico	Cross-sectional (no comparator)	Outpatient (rheumatology)	All <sup>a</sup> : 145 Gout: 5	All: 46 ± 16.1	All: 13.9	ACR criteria	7
Wang, 2010 <sup>36</sup>	Taiwan	Cross-sectional (w/ comparator)	Survey	Gout: 305 No gout: 3665	NR	Gout: 67.9 No gout: 54.8	Self-report	5
Mak, 2011 <sup>34</sup>	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 <sup>39</sup>	USA	Cross-sectional (w/ comparator)	Survey (respondents with HTN)	HTN gout: 1022 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 <sup>24</sup>	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 <sup>25</sup>	Taiwan	Cohort	Administrative health database	Gout: 19,368 No gout: 77,472	Gout: 42.7 ± 12.0 No gout: 42.7 ± 12.0	Gout: 100 No gout: 100	ICD-9	7
Hsu, 2015 <sup>26</sup>	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	7
Kim, 2015 <sup>32</sup>	USA	Cross-sectional (w/ comparator)	Survey	All <sup>b</sup> : 2266	NR	All: 43.5	Self-report	6
Prior, 2015 <sup>27</sup>	UK	Cohort	Outpatient (primary care)	Gout: 1689 No gout: 6756	Gout: 63 ± 16 No gout: NR	Gout: 76 No gout: NR	Read code	8
Branco, 2016 <sup>31</sup>	Portugal	Cross-sectional (w/ comparator)	Survey	Gout: 92 No RMD: 678	NR	NR	ACR criteria	7
Kuo, 2016 <sup>10</sup>	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	7
Prior, 2016 <sup>35</sup>	UK	Cross-sectional (no comparator)	Administrative health database and survey	Gout: 1184	65.6 ± 12.5	81.5	Read code	7
Fu, 2017 <sup>23,c</sup> ; Fu, 2018 <sup>22,c</sup>	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: 94.0	ACR criteria	7
Yin, 2017 <sup>37</sup>	China	Cross-sectional (no Comparator)	Hospital inpatients and outpatients	125	55.2 ± 14.9	94	ACR criteria	7
Chandratte, 2018 <sup>40</sup>	UK	Cross-sectional (no comparator)	Outpatient (primary care)	1184	65.6 ± 12.5	83.6	Read code	7
Scheepers, 2018 <sup>28</sup>	UK	Cohort	Administrative health database	48,280	64.6 ± 13.2	75.7	Read code + allopurinol prescription	7
Singh, 2018 <sup>29</sup>	USA	Cohort	Administrative health database	All <sup>d</sup> : 1,693,515	All <sup>d</sup> : 75.3 ± 7.6	All <sup>d</sup> : 42.9	ICD-9	7
Wändell, 2019 <sup>30</sup>	Sweden	Cohort	Administrative health database	AF gout: 1049 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 <sup>38</sup>	China	Cross-sectional (no comparator)	Survey	186	61.9 ± 10.9	81.2	ACR criteria	7

<sup>a</sup> All: refers to entire study sample with rheumatic diseases (e.g., gout, rheumatoid arthritis). <sup>b</sup> All: refers to every individual from the general population that completed the study survey. <sup>c</sup> Two separate studies using same patient sample, in which 1 evaluated anxiety/depression as determinant of patient outcomes (2017), and 1 evaluated determinants of anxiety/depression (2018). <sup>d</sup> All: refers to the entire study cohort. <sup>e</sup> The maximum quality assessment score was 8 for cohort and 9 for cross-sectional studies. ACR: American College of Rheumatology; AF: atrial fibrillation; ICD-9: International Classification of Diseases, 9th revision; HTN: hypertension; NR: not reported; RMD: rheumatic disease.

gout using billing codes from administrative health databases (e.g., Read codes or ICD codes; n = 10, 50%) or using diagnostic criteria from the American College of Rheumatology (n = 7, 35%). 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%)<sup>10,24–30</sup>, validated screening questionnaires or interviews (n = 10, 50%)<sup>22,23,31–38</sup>, or as a self-reported physician diagnosis (n = 1, 5%)<sup>39</sup>. Studies varied according to the type of screening questionnaire applied to measure depression, and those specifically used were as follows: PHQ-9 (n = 5)<sup>22,23,32,35,37</sup>; Hospital Anxiety and Depression Scale–Depression (HADS-D; n = 2)<sup>31,34</sup>; Center for Epidemiological Studies Depression Scale (CES-D; n = 1)<sup>33</sup>; Geriatric Depression Scale (Short Form; n = 1)<sup>36</sup>; and the 17-item Hamilton Depression Scale followed by structured clinical interview (n = 1)<sup>38</sup>. Reported prevalence proportions for depression in patients with gout, as reported by 12 studies<sup>22,23,25,26,28,30,33,34,35,37,38,39</sup>, ranged from 1.9% to 40%. Prevalence estimates were lowest (1.9% and 2.6%, respectively) in the 2 studies conducted using administrative health data from Taiwan, specifically the National Health Insurance Research Database (NHIRD)<sup>25,26</sup>. In contrast, higher prevalence estimates were presented in studies measuring depression using the PHQ-9 (13–17%)<sup>22,23,35,37</sup>, structured clinical interview using the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (17.2%)<sup>38</sup>, HADS-D (20%)<sup>34</sup>, and self-report (23%)<sup>39</sup>, with the highest estimate reported by a study employing the CES-D (40%)<sup>33</sup>.

A total of 10 studies that evaluated the prevalence of depression included a comparator group comprising individuals without a gout diagnosis<sup>22,23,25,26,30–32,34,36,39</sup>. Two of these studies sampled participants from Taiwan's NHIRD<sup>25,26</sup> using overlapping time periods; therefore, the article reporting on the widest time interval by Hsu, *et al*<sup>26</sup> was selected for metaanalysis. Our metaanalysis, based on more than 38,009 patients with gout (an approximation as 1 study<sup>32</sup> did not provide the sample size for their gout population), resulted in a pooled OR of 1.29 (95% CI 1.07–1.56; Figure 2A). Four studies evaluated the incidence of depression among patients with gout using administrative billing codes to define depression<sup>10,24,27,29</sup>, and findings from our metaanalysis (n > 74,850 gout, n > 113,967 without gout; estimates, as 1 study<sup>29</sup> did not specify sample sizes) yielded a pooled HR of 1.17 (95% CI 1.01–1.36; Figure 2B). Evaluation of the funnel plot (Supplementary Figure 1B, available with the online version of this article) pertaining to HR estimates of depression suggested evidence of publication bias.

**Prevalence and incidence of anxiety.** Compared to depression, anxiety was evaluated less often among patients with gout. Nine

of the 10 included studies on anxiety specifically evaluated prevalence or incidence<sup>22,23,26,27,30,31,34,35,37</sup>. The prevalence of anxiety was most often assessed using the 7-item Generalized Anxiety Disorder (n = 4)<sup>22,23,35,37</sup>, followed by the Hospital Anxiety and Depression Scale–Anxiety (n = 2)<sup>31,34</sup>, and using administrative billing codes (n = 2)<sup>27,30</sup>. 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%. Pooling OR from 5 studies<sup>22,26,30,31,34</sup> (n = 36,682 with gout, n = 82,734 without gout) resulted in an OR of 1.29 (95% CI 0.96–1.73). Pooled estimates from the metaanalysis are shown in Figure 3. Only 1 study using administrative health data estimated the risk of anxiety among patients with gout and reported an adjusted HR of 1.01 (95% CI 0.87–1.16)<sup>27</sup>.

**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 QOL (HRQOL), and sociodemographic characteristics. Indeed, an analysis by Prior, *et al*<sup>35</sup> suggests that oligo/polyarticular gout is positively associated with depression (OR 2.01, 95% CI 1.2–3.3) irrespective of allopurinol use. Stratification by allopurinol use increased estimates pertaining to oligo/polyarticular gout, and also indicated that patients with gout taking allopurinol who reported ≥ 3 gout attacks in the previous 12 months had higher odds of experiencing symptoms of depression compared to patients without gout attacks (OR 2.87, 95% CI 1.2–6.6)<sup>35</sup>. Zhou, *et al*<sup>38</sup> similarly reported that frequency of gout attacks and attacks occurring in multiple joints was associated with increased odds of depression. Additional factors related to gout severity, specifically number of tophi and physical disability, were also associated with increased odds of depression<sup>22</sup>. One of the factors associated with reduced odds of depression symptoms was better QOL, as measured by the mental health component of the Medical Outcomes Study 36-item Short Form survey (SF-36)<sup>22</sup>. A cohort study by Changchien, *et al*<sup>24</sup> further showed that patients with gout taking antigout medications (e.g., colchicine, ULT) had a lower risk of depression. While several gout-specific factors did not have a significant association with anxiety<sup>35</sup>, it was noted by Fu, *et al*<sup>22</sup> that higher education and better SF-36 mental health scores were associated with decreased odds of symptoms of anxiety.

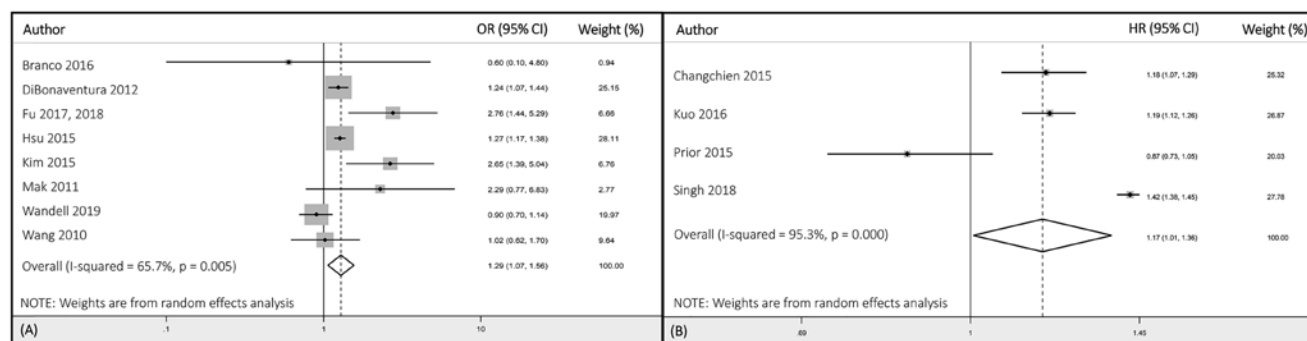


Figure 2. (A) Pooled OR, and (B) pooled HR for depression in patients with gout.



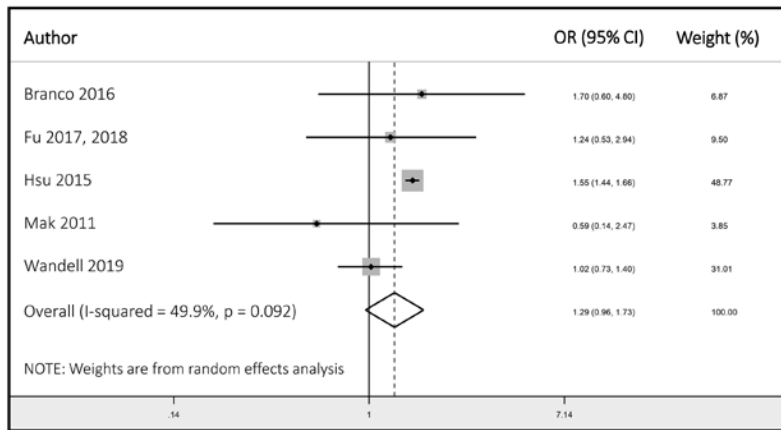


Figure 3. Pooled OR for anxiety in patients with gout.

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

Factor (Author, Yr)	Depression Estimate (95% CI)	Anxiety Estimate (95% CI)
<b>Gout-specific factors</b>		
Frequency of gout attacks (Prior, 2016 <sup>35</sup> )		
1–2 gout attacks (ref. 0)	allopurinol aOR 1.49 (0.70–3.40) no allopurinol aOR 0.64 (0.20–1.90)	allopurinol aOR 0.76 (0.30–1.80) no allopurinol aOR 0.57 (0.20–1.80)
≥ 3 gout attacks (ref. 0)	<b>allopurinol aOR 2.87 (1.2–6.6)</b> no allopurinol aOR 1.16 (0.3–4.1)	allopurinol aOR 1.72 (0.7–4.3) no allopurinol aOR 2.07 (0.6–7.4)
Oligo/polyarticular gout (Prior, 2016) (reference: no oligo/polyarticular gout)		
Gout duration, yrs (Prior, 2016)		
3–8 (ref. ≤ 2 yrs)	allopurinol aOR 1.27 (0.40–3.80) no allopurinol aOR 0.46 (0.20–1.30)	allopurinol aOR 0.96 (0.30–3.30) no allopurinol aOR 0.57 (0.20–1.60)
9–17 years (ref. ≤ 2 yrs)	allopurinol aOR 2.11 (0.70–6.40) no allopurinol aOR 0.45 (0.10–1.70)	allopurinol aOR 1.90 (0.60–6.30) no allopurinol aOR 0.34 (0.10–1.40)
≥ 18 years (ref. ≤ 2 yrs)	allopurinol aOR 2.11 (0.7–6.3) no allopurinol aOR 0.92 (0.3–3.2)	allopurinol aOR 2.99 (0.9–9.8) no allopurinol aOR 0.77 (0.2–3.1)
No. tophi (Fu, 2018 <sup>22</sup> )	<b>aOR 1.74 (1.05–2.90)</b>	
Antigout medication (Changchien, 2015 <sup>24</sup> )	<b>aHR 0.70 (0.55–0.88)</b>	
Frequent gout attacks (≥ 3) (Zhou, 2019 <sup>38</sup> )	<b>aOR 6.14 (1.74–21.67)</b>	
Gout attacks in multiple joints (Zhou, 2019)	<b>aOR 4.45 (1.45–13.51)</b>	
<b>Clinical characteristics</b>		
Disability: HAQ-DI (Fu, 2018)	<b>aOR 3.62 (1.61–8.18)</b>	
HRQOL: SF-36 MCS (Fu, 2018)	<b>aOR 0.94 (0.91–0.98)</b>	<b>aOR 0.87 (0.80–0.94)</b>
25-hydroxyvitamin D, ≤ 40.0 nmol/L, (Zhou, 2019)	<b>aOR 3.83 (1.41–10.45)</b>	
<b>Sociodemographic characteristics</b>		
Education (Fu, 2018)		<b>aOR 0.16 (0.03–0.86)</b>
Age (Zhou, 2019)	aOR 0.99 (0.95–1.03)	
Sex (Zhou, 2019)	aOR 1.01 (0.32–3.18)	

Values in bold face are significantly associated with depression or anxiety. aHR: adjusted HR; aOR: adjusted OR; HAQ-DI: Health Assessment Questionnaire–Disability Index; HRQOL: health-related quality of life; SF-36 MCS: Medical Outcomes Study 36-item Short Form survey mental component summary.

**Effects of depression and anxiety.** Six studies, using cross-sectional ( $n = 3$ )<sup>23,37,40</sup> and cohort ( $n = 3$ )<sup>25,26,28</sup> 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 are significantly associated with QOL for patients living with gout, specifically reporting a lower HRQOL and higher functional limitations when compared to patients with gout without

depression or anxiety<sup>23,40</sup>. Last, a 2015 cohort study by Hsu, *et al*<sup>26</sup> that included 35,265 men with gout found that both depression and anxiety in the context of gout were associated with an increased risk of erectile dysfunction.

## DISCUSSION

From our systematic review that included 20 articles describing the burden, risk, determinants, and effects of depression and

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

Outcome (Author, Yr)	Depression (95% CI)	Anxiety (95% CI)
<b>HRQOL</b>		
SF-36 MCS (Fu, 2017 <sup>23</sup> )	$\beta$ -14.27 (-22.09 to -6.45)	$\beta$ -13.45 (-25.48 to -1.43)
SF-36 PCS (Fu, 2017)	$\beta$ -16.65 (-23.93 to -9.37)	
SF-36 PCS (Chandratre, 2018 <sup>40</sup> )	$\beta$ -1.98 (-2.24 to -1.71)	$\beta$ -1.81 (-2.14 to -1.47)
GIS CO (Chandratre, 2018)	$\beta$ 0.84 (0.50 to 1.19)	$\beta$ 0.88 (0.50 to 1.26)
GIS MSE (Chandratre, 2018)	$\beta$ 1.07 (0.72 to 1.42)	$\beta$ 1.11 (0.72 to 1.50)
GIS UTN (Chandratre, 2018)	$\beta$ 0.42 (0.16 to 0.69)	$\beta$ 0.38 (0.08 to 0.68)
GIS WBDA (Chandratre, 2018)	$\beta$ 1.47 (1.13 to 1.82)	$\beta$ 1.44 (1.05 to 1.82)
GIS CDA (Chandratre, 2018)	$\beta$ 1.47 (1.16 to 1.78)	$\beta$ 1.70 (1.36 to 2.05)
<b>Disability</b>		
HAQ-DI (Fu, 2017)	$\beta$ 2.11 (3.57 to 19.23)	
HAQ-DI (Chandratre, 2018)	$\beta$ 0.06 (0.05 to 0.07)	$\beta$ 0.06 (0.05 to 0.07)
<b>Comorbidities</b>		
Erectile dysfunction (Hsu, 2015 <sup>26</sup> )	aHR 2.01 (1.53 to 2.65)	aHR 1.50 (1.15 to 1.97)

aHR: adjusted HR; 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 summary; SF-36 PCS: 36-Item Short Form survey, Physical Component Score.

anxiety for patients with gout, we found that the odds of individuals with gout presenting symptoms of depression increased by 29%, and, while nonsignificant, the odds of having symptoms of anxiety increased by 29%. Although there are fewer studies reporting on the risk of incident depression and anxiety following a gout diagnosis, our resultant metaanalyses suggested a 17% increased hazard for depression. Importantly, several determinants of depression and anxiety in patients with gout were identified, which included oligo/polyarticular gout and number of tophi for depression, as well as QOL and education for anxiety<sup>22,35</sup>. Overall, findings from our synthesis emphasize that patients with gout have an elevated burden of mental disorders; as such, depression and anxiety should also be monitored when managing patients with gout.

Prior to our systematic review, Lin, *et al*<sup>18</sup> published a systematic review that metaanalyzed various point estimates (e.g., OR and HR) from 7 studies, and their findings indicated a positive association between gout and depression with a resultant OR of 1.19 (95% CI 1.11–1.29). 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 compared to controls, we conducted distinct metaanalyses according to the study design, hence the reported point estimate. Our results suggest that patients with gout have increased odds of experiencing symptoms affecting their mental health, with equivalent pooled OR for depression (OR 1.29, 95% CI 1.07–1.56) and anxiety (OR 1.29, 95% CI 0.96–1.73), although the CI for the latter estimate did not reach significance. In addition, estimates pertaining to the prevalence of depression and anxiety among patients with gout ranged from 1.9% to 40% and 3.8% to 10%, 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 with RA, where the pooled prevalence of depression based on 659 patients with RA according to the PHQ-9 is 38.8% (95% CI 34.0–43.0)<sup>12</sup>, 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%<sup>37</sup>. 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<sup>41,42</sup>, 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 included studies that evaluated the risk of mental disorders after a diagnosis of gout. A total of 4 articles identified from our search published adjusted estimates describing the risk of depression in patients with gout that, when metaanalyzed, indicated a 17% increased risk for incident depression (HR 1.17, 95% CI 1.01–1.36). Interestingly, Kuo, *et al*<sup>10</sup> found that, as with other comorbidities, the cumulative probability of incident depression increased over time in comparison to matched controls, specifically doubling over a 10-year period from the time of diagnosis for patients with gout. A 2018 study by Singh, *et al*<sup>29</sup> based on a US Medicare sample ( $\geq$  65 yrs of age) was the most recent cohort study measuring incident depression included in our review, and reported a 42% increased risk (HR 1.42, 95% CI 1.38–1.45) of incident depression among patients with gout 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 compared to men<sup>29</sup>. 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 women (OR 5.00, 95% CI 1.26–19.82) but was nonsignificant for men (OR 1.43, 95% CI 0.57–3.55)<sup>32</sup>. Though gout predominately affects more men than women<sup>2,3</sup>, the observation that more women experience

depressive symptoms in the context of gout is reflective of current literature for the general population showing that up to 2-times more women than men experience mental disorders such as depression and anxiety<sup>43,44</sup>. 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 healthcare and men to be undertreated<sup>45,46</sup>. Finally, even though anxiety is one of the most common mental disorders, affecting approximately 3.6% of the global population<sup>47</sup>, our review retrieved only 1 article on the incidence of anxiety and this UK study showed no significant risk for incident anxiety in patients with gout<sup>27</sup>. 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 effect 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. Several modifiable risk factors associated with depression were relevant to clinical practice and can be addressed through improving quality of care for gout, which is persistently suboptimal<sup>48,49,50,51</sup>. Studies consistently report insufficient prescribing and monitoring of antigout medications<sup>50,52</sup> highlight low adherence to ULT<sup>5</sup> and consequently note an insufficient proportion of patients reaching target serum urate (SUA) levels<sup>50,51</sup>. 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<sup>22,35</sup>. Our systematic review also identified 1 cohort study that showed taking antigout medications (e.g., colchicine, uricosuric agents, xanthine oxidase inhibitors) is associated with a 30% decreased risk of incident depression<sup>24</sup>. Therefore, improving quality of care for gout extends beyond addressing disease severity and treatment adherence, and is closely integrated with affecting 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 5 international reference databases. An additional strength of our review was that data extraction and metaanalyses 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, since our inclusion criteria were restricted to peer-reviewed full-text publications. This review focused on the epidemiology of depression and anxiety because 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<sup>52</sup>.

As demonstrated in our systematic review, patients with

gout experience an increased likelihood of having comorbid depression and anxiety 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<sup>53</sup>, our findings have implications for clinical practice as healthcare 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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#### ONLINE SUPPLEMENT

Supplementary material accompanies the online version of this article.

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