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Healthcare burden of depression in adults with arthritis

Usha Sambamoorthi, **Drishti Shah**, and **Xiaohui Zhao**

Department of Pharmaceutical Systems and Policy, School of Pharmacy, West Virginia University, Morgantown, WV, USA

Abstract

Introduction—Arthritis and depression are two of the top disabling conditions. When arthritis and depression exist in the same individual, they can interact with each other negatively and pose a significant healthcare burden on the patients, their families, payers, healthcare systems, and society as a whole.

Areas covered—The primary objective of this review is to summarize, identify knowledge gaps and discuss the challenges in estimating the healthcare burden of depression among individuals with arthritis. Electronic literature searches were performed on PubMed, Embase, EBSCOhost, Scopus, the Cochrane Library, and Google Scholar to identify relevant studies.

Expert Commentary—Our review revealed that the prevalence of depression varied depending on the definition of depression, type of arthritis, tools and threshold points used to identify depression, and the country of residence. Depression exacerbated arthritis-related complications as well as pain and was associated with poor health-related quality of life, disability, mortality, and high financial burden. There were significant knowledge gaps in estimates of incident depression rates, depression attributable disability, and healthcare utilization, direct and indirect healthcare costs among individuals with arthritis.

Keywords

Depression; arthritis; burden; prevalence; incidence; morbidity; health-related quality of life; disability; mortality; economic burden

1. Introduction

Arthritis includes many conditions that affect joints, the tissues surrounding the joints, and other connective tissues [1]. Although a worldwide prevalence of arthritis among adults is not available, prevalence estimates from selected countries show wide variations. The reported prevalence varies from 4% in Japan, 8.5% in the Netherlands, 17% in Germany, and 40.5% in Italy [2]. In 2012, the prevalence of arthritis in the USA was estimated to be 22.7%

CONTACT Usha Sambamoorthi usambamoorthi@hsc.wvu.edu, Pharmaceutical Systems and Policy, 1 Medical Center Drive, Morgantown, WV 26506.

Declaration of interest

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(52.5 million adults over 18 years of age) and projected to increase to 49% (about 78 million Americans) by 2040 [3].

There are more than 100 types of arthritis [4]. The most common types can be split into three main groups, including degenerative arthritis, inflammatory arthritis, and metabolic arthritis [5]. Degenerative arthritis, which is commonly known as osteoarthritis (OA), refers to a group of conditions involving damages to the cartilage that covers the ends of the bones, causing the cartilage to become thinner and rougher [5]. OA is the most common form of arthritis, affecting approximately 31 million adults in the USA [6]. Inflammatory arthritis is characterized by damaging inflammation that does not occur as a normal reaction to injury or infection, which can cause damage in the affected joints, tissues surrounding the joints, and the underlying bone [5]. The most common form of inflammatory arthritis is rheumatoid arthritis (RA), which affects 1.5 million US adults [7]. Other commonly seen inflammatory arthritis include psoriatic arthritis (0.16%) [8] and systemic lupus erythematosus (0.07 – 0.13%) [9]. Metabolic arthritis, also known as gout, is one of the most painful forms of arthritis, affecting more than eight million adults in the USA [10]. It is caused by high levels of uric acid in the blood, which settles as crystals in the tissues of the joints and produce severe pain and swelling.

All forms of arthritis can be highly disabling. Arthritis is the leading cause of disability among adults in the USA [11] and elsewhere [12]. A report using data from the National Health Interview Survey (NHIS), a nationally representative survey of civilian noninstitutionalized US households indicated that 43.2% of adults had arthritis-attributable activity limitations [13]. Chronic pain and disabilities associated with arthritis may lead to negative psychological effects ranging from sadness to depressive symptoms to clinical depression [14], hereafter referred to as depression. Depression can impose a significant disease burden among individuals with arthritis. The purpose this article is to summarize, identify knowledge gaps, and discuss the challenges in estimating the excess burden of depression among individuals with arthritis. The current paper also provides directions for future research.

Electronic literature searches were conducted on EMBASE, EBSCOhost, PubMed, Medline, PsychInfo, Scopus, Google Scholar, and CINAHL databases from 2000 to 2016. We used the following keywords: ‘depression and arthritis,’ ‘arthritis,’ ‘osteoarthritis,’ ‘rheumatoid arthritis,’ ‘gout,’ ‘depression,’ and ‘depressive disorder.’ To identify the relationship between depression and arthritis in specific areas, we used the search terms ‘health-related quality of life,’ ‘disability’, ‘costs’, and ‘economic burden’. Existing reviews and references of identified studies were also scanned for additional references. It should be noted that this review is not meant to systematically review all the studies that have ever been conducted in the area of depression and arthritis.

2. Burden of depression among individuals with arthritis

Disease burden is commonly measured using a variety of indicators such as morbidity, mortality, and cost [15]. Two important metrics of morbidity is the prevalence and incidence

of a disease [16]. Therefore, we first examine the prevalence of depression among individuals with arthritis.

3. Prevalence of depression among individuals with and without arthritis

Depression is more prevalent among individuals with arthritis compared to those without arthritis [17–19]. A community-based study of Canadian adult residents reported that individuals with arthritis were almost two times as likely to have depression as compared to those without arthritis [20]. A US study using the 2002 NHIS data estimated that 26.2% adults with arthritis had depression compared to 10.7% adults without arthritis [17]. Results from the World Health Survey (WHS) administered by the World Health Organization (WHO), which studied 245 404 participants from 60 countries across the world, indicated that the prevalence of depression in respondents with arthritis was significantly higher than in those without arthritis (10.7% vs. 3.2%, $p < 0.0001$) [21].

As studies often examine the prevalence of depression by type of arthritis, we describe the prevalence of depression by RA, OA, and other forms of arthritis (Table 1).

3.1. Depression and OA

The reported prevalence of depression ranged from as low as 4.1% [90] to as high as 61.3% in individuals with OA [88]. A meta-analysis examined prevalent depression among 10,811 adults from 24 studies. The meta-analysis estimated the pooled prevalence at 19.9% [95% Confidence Interval (CI): 15.9–24.5%, $I^2 = 96.1\%$] [122]. In subgroup analyses, the study also estimated prevalent depression by types of OA. The pooled prevalence of depression among knee OA patients (18.5%, 95%CI: 13.8–23.7%, $I^2 = 95.4\%$) was lower than that among mixed hip/ knee OA patients (23%, 95% CI: 16.4–30.2%, $I^2 = 95.8\%$). However, only a handful of studies have compared the prevalence of depression among individuals with and without OA [90,91,104,110,123]. Three studies did not find statistically significant difference in prevalence of depression among individuals with and without OA [122]. A recent study that compared individuals with OA and age- and sex-matched healthy controls found a higher prevalence of depression among individuals with OA (49.3% vs. 12.3%) [104]. These findings suggest that the association between OA and depression remains inconclusive.

3.2. Depression and RA

Among individuals with RA, the reported prevalence of depression varied from 4.0% [43] to 66.2% [28]. The results of a meta-analysis examining the prevalence of depression among 13,189 individuals from 72 studies revealed that the pooled prevalence of depression was 16.8% (95%CI: 10–24%, $I^2 = 73.4\%$) [124]. The majority of the studies included in the meta-analysis did not compare depression prevalence among individuals with and without RA. Studies that compared individuals with and without RA consistently reported higher depression rates among individuals with RA. For example, one study reported that individuals with RA had a higher prevalence of depression (47.5%) compared to age-matched healthy controls (5.6%) [125]. Similar results were reported by another individual study and an early meta-analysis [24,126]. Even when prevalent depression is examined by

type of arthritis (OA and RA), it was consistently found that individuals with RA had higher rates of depression than those with OA [30,77,78].

3.3. Depression and other forms of arthritis

Studies estimating the prevalence of depression among adults with other forms of arthritis are scant. A handful of studies reported higher depression prevalence in individuals with SLE as compared to those without SLE [119,121,127]. A few studies estimated the prevalence of depression at 13% [115] and 60% [117] among adults with SLE. A retrospective cohort study of UK adults reported that 12.6% of individuals with gout were diagnosed with depression in the primary care settings [128]. A Canadian study comparing the prevalence of depression among individuals with SLE and RA found a marginally higher rate among individuals with SLE as compared to those with RA (6% versus 4%) [43].

3.4. Plausible reasons for variations in prevalence estimates of depression

Several reasons may explain the variations in the prevalence of depression among adults with arthritis. First, the absence of bio-markers to diagnose depression makes it challenging to detect depression among arthritis patients because the somatic symptoms of depression such as fatigue, pain, and insomnia mimic those of arthritis. Second, depression is identified using different tools such as Diagnostic and Statistical Manual of Mental Disorders-Fourth Edition (DSM-IV) [129], interviewer and self-administered depression scales [130]. Third, studies have examined different types of depression. Some studies examined clinical depression, also known as major depressive disorder (MDD), whereas others did not distinguish between types of depression.

3.5. Variations in measurements of depression

The ‘golden standard’ used to diagnose depression is a structured clinical interview by physicians using the DSM criteria. Due to the time-intensive nature of the interview, only a few studies have utilized this ‘golden standard’ [122,124]. Studies using DSM-III/IV have typically found relatively low prevalence (14–41.5%) [24,131]. Depression identified in the clinical setting and covered by health insurers are often captured in insurance claims databases by the International Classification of Diseases (ICD) codes [132]. Studies using claims databases reported depression prevalence varying from 7.5% to 66.2% [28,29]. Patients with depression can also be diagnosed with self-report screening scales administered in a clinical setting [133,134]. The reported prevalence of depression from self-rating scales varied from 4% to 60% [43,58,90,117]. At least nine self-administering scales were used to identify depression among individuals with different types of arthritis. These were: the Beck Depression Inventory (BDI), the General Health Questionnaire (GHQ-28), the Patient Health Questionnaire (PHQ), the Hospital Anxiety and Depression Scale (HADS), the Center for Epidemiologic Studies Depression Scale (CES-D), the Zung self-rating depression scale (Zung-SRS), the Geriatric Depression Scale (GDS), the Depression, Anxiety and Stress Scale (DASS), and the Hamilton Depression Rating Scale [122,124]. Among these scales, the HADS, CES-D, and the BDI were most commonly used. Within studies using HADS, CES-D, and BDI to identify depressive cases, the prevalence ranged from less than 1% [135] to 55.8% [136], 7.4% [59] to 60% [58], and 11.4% [102] to 66.3% [79], respectively.

Even when studies were restricted to the same type of arthritis and same depression screening tool, variations in depression prevalence still remained. Among the studies applying the HADS, the reported prevalence of depression ranged from 0% [135] to 55.8% [136], 4.1% [90] to 40.7% [92], and 13% [115] to 31.5% [116] among individuals with RA, OA, and SLE, respectively. Among the studies using the CES-D, the prevalence of depression ranged from 7.4% [59] to 60% [58], and 9.7% [97] to 46% [98] among individuals with RA and OA, respectively. Within studies employing the BDI, the prevalence of depression varied from 26.5% [77] to 63.3% [74], 11.4% [102] to 49.3% [104], and 16.6% [137] to 60% [117] among individuals with RA, OA, and SLE, respectively. A limited number of studies have compared the prevalence of depression in the same study sample with more than one scale. One study assessing the variability in measuring depression with the CES-D and HADS among individuals with early RA indicated that the two scales measured the same underlying construct; however, the difference in their thresholds led to variations in the prevalence of depression [138].

3.6. Variations in thresholds in detecting depression

When using depression scales, often the values from individual items are summed and a predetermined threshold is used to detect depression. The sensitivity and specificity rates of the scales may vary depending on the thresholds [130]. As depression scales were not originally developed for detecting depression among individuals with arthritis, no consensus has been reached on using a specific threshold to maximize sensitivity and specificity. When the HADS with a threshold of eight was used to determine the prevalence of depression among adults with RA and OA, the prevalence estimates ranged from 20% [32] to 55.6% [28], and 4.1% [90] to 40.7%, respectively [92]. When using a threshold of ten, both the reported rates and the variation decreased in RA (0–25.6%) [32,40] and OA (5.6–8.3%) [95,96]. When using the CES-D with a threshold of 16, higher prevalence of depression was found in general; but varied among individuals with RA (23.5–60%) [58,59] and OA (9.7–46%) [97,98].

3.7. Variations in depression in selected countries

We also observed high intercountry variability in the prevalence of depression among individuals with arthritis. The prevalence of depression ranged from 4% in Canada to 66.3% in Egypt among individuals with RA [28,43], 4.1% in Taiwan to 61.3% in Brazil among individuals with OA [88,90], and from 15% in China (Mainland) to 45.2% in the Thailand among individuals with SLE [114,139]. Further, international studies examining the prevalence of depression among individuals with arthritis also reported substantial variations [140]. A recent international study among 3,920 individuals with RA from 17 countries indicated that the self-reported prevalence of depression can be as low as 2% in Morocco to as high as 33% in the USA [140]. Another study including individuals with RA from Germany and Brazil reported significantly higher prevalence among individuals in Germany compared to residents of Brazil (20% vs. 10%, $p = 0.039$) [141]. However, it is difficult to discern whether the country-level differences are due to differences in various diagnostic tools or cultural differences or varying levels of stigma associated with depression.

4. Incident depression and arthritis

As arthritis imposes a heavy physical, psychological, and economic burden [142], many individuals may develop depression after arthritis diagnosis, known as incident depression. Individuals with arthritis were three times as likely to report moderate-to-severe pain compared to individuals with other chronic conditions and pain can trigger incident depression [33,81,143]. On the other hand, those with depression may experience pain, suggesting that the causal relationship between depression and pain can be bidirectional [144–148]. Studies in the USA, Canada, and Japan provide evidence to this bidirectional relationship between depression and pain in individuals with RA [144–146]. Regardless of the causal pathways between depression and pain, individuals with arthritis may be at risk for developing depression.

However, studies examining incident depression among individuals with arthritis are sparse. It may be difficult to estimate incident depression among individuals with arthritis due to the bidirectional relationship between depression and pain. Only a few studies, most of which examined adults with RA using retrospective and observational study designs, have reported estimates of incident depression. For example, one study examined incident depression using an observational longitudinal database, namely the Consortium of Rheumatology Researchers of North America (CORRONA) registry. This registry contained the history of 33,000 US adults with physician-diagnosed RA between October 2001 and August 2012. This study reported that all the measures of disease activity were associated with incident depressive symptoms [149]. The study, however, did not report how many individuals with RA developed depressive symptoms [149]. A seven-year population-based cohort study based on the Taiwan's National Health Insurance Research Database reported that incidence of depression was 1.74 times as likely among individuals with RA as those without RA[150]. A study that used the same database with a longer follow-up period (10 years) reported that individuals with RA were 2.06 times as likely to develop depressive disorders (95% CI: 1.73–2.44, $p < 0.001$) as those without RA, after adjusting for age, sex, and comorbidities. Further, among individuals with RA, most depressive disorders developed within five years after RA diagnosis [151]. When examining a cohort of 1,609 individuals with no prior history of depression and SLE, it was found that incidence of depression was as high as 29.7 episodes per 1000 person-years [152].

The pathophysiological mechanisms linking depression and arthritis are complex and remain unclear [153]. Some investigations have suggested that proinflammatory biomarkers such as cytokines and C-reactive protein may be associated with depression [154,155]. Because of the relationship between inflammation and depression, the risk of depression may be increased among individuals with inflammatory illnesses such as RA [126]. There is evidence that depression in individuals with RA may be due to the systemic inflammation resulting from the proinflammatory cytokine milieu of RA [156]. However, other studies have reported that the depression and RA may be linked through the dysfunctional neuroendocrine system [156,157]. Empirical reviews have also suggested that the intracellular pathways, including PI-3K/AKT/mTOR and stress- and mitogen-activated protein kinases (SAPK/MAPK), may explain the connection between the two chronic conditions [158,159]. The mechanisms of developing depression in OA may be different

because OA is often considered as a noninflammatory arthritis. However, recent findings and interpretations indicate that OA can be classified as an inflammatory disease because of joint inflammation and synovitis [154]. Therefore, the same inflammatory mechanism may explain the association between depression and OA.

Given that the inflammatory markers are common among individuals with depression or arthritis, one can speculate that depression may be associated with incident arthritis. For example, a longitudinal cohort study reported that individuals with depression had 1.3 times [Hazard Ratio (HR) = 1.3, 95%CI: 1.0–1.7] of the risk of developing arthritis as compared to those without depression [160]. Further, a 14-year, population-based cohort study reported significantly higher incidence (HR = 1.65, 95%CI: 1.41–1.77) of RA among individuals with depression as compared to those without depression [161].

5. Morbidity due to depression among adults with arthritis

Disease burden among individuals with arthritis and depression can also be measured by health-related quality of life (HRQoL) and disability. Therefore, we also reviewed studies on the burden of depression among individuals with arthritis in terms of HRQoL and disability.

5.1. Health-related quality of life and depression

HRQoL is a multidimensional concept that includes physical, mental, emotional, and social functioning of an individual [162]. HRQoL instruments have gained importance in evaluating the morbidity associated with a particular disease as one can numerically quantify the burden of a disease on a person's overall well-being [162,163]. Results from a study examining the HRQoL associated with chronic conditions in eight countries (Denmark, France, Germany, Italy, Japan, the Netherlands, Norway, and the USA) found that arthritis had higher impact on an individual's HRQoL compared to the general population [2]. This finding suggests that adults with arthritis have lower HRQoL compared to those without arthritis. Similarly, adults with depression were found having lower HRQoL compared to those without depression [164–167]. The Medical Outcomes Study compared the social well-being and physical functioning of individuals with depression with those of other chronic conditions [168]. This study showed that as compared to other chronic medical conditions, depression had the greatest negative impact on a patients' HRQoL. Therefore, individuals with coexisting depression and arthritis may have worse HRQoL as compared to those with either of the diseases alone.

HRQoL instruments can be either generic or disease specific. All the studies mentioned in this review that assessed the impact of depression on HRQoL among individuals with arthritis used generic instruments. Commonly used generic HRQoL instruments included: 36-item Short Form (SF-36), the 12-item Short Form (SF-12), the Nottingham Health Profile (NIH), the EuroQoL (EQ-5D), and the Sickness Impact Profile [169].

Using these generic instruments, it has been reported that among individuals with arthritis, depression can worsen their HRQoL [169]. The majority of the studies were restricted to individuals with RA [170–174]. A cross-sectional study using data from the Behavioral Risk Factor Surveillance System (BRFFS), a nationally representative survey of adults in the

USA, found that among adults with arthritis, those with depression had lower general health status, physical, and mental HRQoL compared to those without depression [175]. This study used a single-item measure for each of the HRQoL domains: physical, mental, and general health status [163]. Studies in Turkey, Korea, Italy, and Egypt have also demonstrated poor HRQoL among individuals with arthritis and depression [171–173,176]. A Turkish study conducted among individuals with RA, knee OA, and fibromyalgia syndrome (N = 154) reported that those with depression (identified with the BDI) had significantly lower scores across all domains of the SF-36 scale [140]. Another study conducted in Turkey, which assessed HRQoL among adults with RA (N = 100), using the Nottingham Health Profile (NHP), found significant associations between all subgroups of NHP and higher BDI scores [172]. A Korean study conducted among 131 individuals with RA concluded that depression, rather than pain and disease activity, had profound impact on HRQoL measured by the SF-36 [171]. Another study examining 92 individuals with RA in Italy found that depressive symptoms contributed to significant impairment of both the physical and mental health domains of HRQoL (measured by the SF-36), even after controlling for a comprehensive set of covariates such as functional limitations, duration of illness, and demographic characteristics [173]. When HRQoL was measured using the SF-12, it was found that women with depression and RA had lower HRQoL scores compared to those without RA and without depression. The findings of this study are limited because the study sample was restricted to women in one region of the USA and therefore lacked generalizability [170]. To summarize, depression was found to negatively affect the HRQoL of individuals with RA.

5.2. Disability due to depression among adults with arthritis

Disability is a commonly used measure of disease burden [177]. Although there are diverse measures of disability [178], the conceptual framework of the International Classification of Functioning and Disability can be used to describe disability and functioning. Under the ICF framework, disability is broadly defined as ‘impairments, activity limitations, and participation restrictions’ [163]. Disease burden is sometimes measured in terms of years lived with disability (YLDs) [177]. According to the Global Burden of Disease (GBD) investigators, major depression ranked among the top-three leading causes of disability (based on YLDs) in 188 countries in 2013 [179]. Arthritis, by itself can be a risk factor for disability. One study examining the data from the NHIS reported that almost 10% of adults had arthritis-attributable activity limitation during 2010–2012, and the number would increase to 52% by 2040 [3]. In addition to activity limitations, 31% (8.3 millions) of working-age adults with arthritis reported being limited in work due to arthritis [180]. According to the 2009 NHIS data, more than 40% of adults with arthritis reported difficulties or failure in performing at least one of the nine important daily functional activities such as grasp, reach, and sit [181]. It has been highlighted that the disability among individuals with arthritis and depression exceeded the disability level one would expect from simply combining the disability associated with arthritis and depression alone [182,183]. Therefore, we can conclude that the negative impact of depression on disability among individuals with arthritis is multiplicative, rather than additive [183].

Using the above-mentioned definitions of disability, studies have examined the association between depression and disability among individuals with arthritis. Several studies have reported that depression is a strong predictor of work disability, disease activity, and response to therapy among adults with arthritis [184]. A recent study using the 2011 BRFSS data found that individuals with coexisting arthritis and depression were less likely to engage in physical activity (OR = 1.07, 95%CI: 1.01–1.14) and more likely to be disabled [Odds Ratio (OR) = 1.41, 95% CI: 1.31–1.52], have higher joint limitations (OR = 1.55, 95% CI: 1.46–1.65), work limitations (OR = 1.51, 95% CI: 1.41–1.60), and limitations in social activities (OR = 1.65, 95% CI:1.56–1.74) as compared to those with arthritis alone [175]. Similar association between depression and disability can be found in all types of arthritis. Depression was found to be significantly associated with functional disability among individuals with RA [74,185]. In addition, even individuals' level of depressive symptoms was found correlated with the level of functional ability [186]. Data from an interventional pilot study indicated that depressive symptoms had moderate effects on the social and role limitations among individuals with SLE [187]. While depression is associated with disability in all types of arthritis, the level of disability due to depression may vary based on the type of arthritis. Depression has been associated with higher disability among adults with RA when compared to those with OA [184].

6. Mortality and depression among adults with arthritis

Depression may not only increase morbidity among adults with arthritis but may also contribute to excess mortality risk. Numerous studies have provided evidence of excess risk of mortality due to depression. Cuijpers et al. conducted a meta-analysis to quantify the risk of mortality by comparing individuals with and without depression. The researchers pooled nearly 1.8 million adults over 18 years of age from 293 studies across 35 countries and concluded that adults with depression were at a higher risk [Relative Risk (RR) = 1.52; 95% CI = 1.45–1.59] for all-cause mortality compared to those without depression [188]. When analyzed by cause of death, suicide accounted for nearly 19% of the mortality in the samples drawn from inpatient or outpatient psychiatric service settings [189].

Among individuals with RA, the risk of mortality in those with clinical depression was 2.2 times higher (RR = 2.2; 95% CI: 1.2–3.9, p = 0.01) than those without depression [190]. In the USA, a comparative study of suicidal ideation among individuals (age ≥40 years) with arthritis, diabetes, or cancer was conducted among participants enrolled in the 2007–2008 National Health and Nutrition Examination Survey (NHANES). In this study, it was reported that the prevalence of suicidal ideation was higher in adults with arthritis (5.6%) compared to those with cancer (5.1%) [191]. Among adults with arthritis, after adjusting for duration of arthritis, drinking, income, pain, coexisting conditions and a comprehensive list of other risk factors, adults with depression were at the greatest risk for suicidal ideation as compared to those without depression [191]. Treharne et al. reported that the rate of suicidal ideation among hospital outpatients with RA and depression was much higher than those with RA and no depression (30% versus 11%) [192]. A study by Timonen et al. linked depression to be an independent risk factor for mortality (non-suicide) in individuals with RA [193]. Further, a study by Ang et al. revealed that depression increased the risk of mortality [HR =

1.35, $p < 0.00001$] in individuals with RA [190]. However, there is a dearth of literature on studies focusing on OA, the most common type of arthritis.

7. Economic burden associated with depression among adults with arthritis

High rates of morbidity associated with depression among adults with arthritis can also exacerbate the economic burden of the patients and their families, payers, and society. The economic burden can be measured with direct costs, indirect costs, and intangible costs that are typically analyzed from payer's, patient's, patient's families', or societal perspectives [194]. Direct costs measure the costs associated with medical resource utilization for treating a particular illness [195]. Direct costs include direct medical costs related to the consumption of inpatient, outpatient, and pharmaceutical services and direct nonmedical costs include transportation costs to healthcare providers, relocation expenses, capital costs, and costs of making changes to one's diet, house, or related items [25,195]. Indirect costs are not directly accountable by the disease or illness and typically include costs attributable to loss of productivity, mortality, and morbidity costs due to absenteeism and presenteeism [22,25,34]. Although some studies include intangible costs such as costs of suffering and pain due to a particular illness, this category of cost is seldom measured and is often omitted because of the difficulty in accurately measuring and quantifying them in monetary terms [194].

It is important to examine the economic burden of depression among individuals with arthritis as there is considerable evidence that individuals with depression use more medical services and have higher healthcare costs than those without depression [22,193–195]. Depression may exacerbate arthritis-related symptoms and increase the need for expensive treatment regimens [22,32,196,197]. It is reasonable to expect individuals with arthritis and depression to have higher direct and indirect costs than those with arthritis and no depression. Furthermore, individuals with coexisting arthritis and depression may have poor medication adherence compared to those with arthritis and no depression, leading to higher costs [142,198]. Therefore, depression is likely to increase the inpatient, outpatient, prescription drug costs, and ER use among individuals with arthritis.

However, few studies have exclusively estimated the excess cost burden associated with depression among arthritis patients. Joyce et al. examined direct healthcare cost of comorbid depression among individuals with RA using retrospective claims data. These investigators found that the mean annual total healthcare costs for coexisting RA and depression were 7.2% higher than those for RA alone. Further, the diagnosis of depression significantly affected RA-related utilization patterns [29]. Another retrospective population-based study estimated that adults with OA and depression had 38.8% higher direct healthcare expenditures as compared to those with OA but without depression [89]. These studies suggest that depression increases direct healthcare expenditures among those with arthritis. We could not find any studies that analyzed depression-attributable indirect costs among individuals with arthritis.

8. Expert commentary

In summary, our exhaustive review highlights the substantial disease burden of depression among individuals with arthritis regarding prevalence and incidence of depression and the effect of depression on HRQoL, disability, mortality, and health-care costs. Our review also notes many challenges to estimating the excess burden of depression among individuals with arthritis. First, we observed wide variations in depression prevalence among individuals with arthritis. Combining all forms of arthritis, the prevalence of depression varied from as low as 4.0% [43] to as high as 66.2% [28]. These differences in rates may be due to many factors: differences in defining depression, type of arthritis, tools used to detect depression, use of different thresholds with the same tools, and country of residence.

Second, as stated in the introduction, arthritis includes many conditions such as OA, RA, and others (e.g. gout and SLE). There are many studies on the prevalence of depression in RA or OA; however, there is a limited number of studies that include all forms of arthritis or other forms of arthritis. We also observed that the relationship between OA and depression remained inconclusive when studies compared the prevalence of depression among adults with and without OA [104,122]. However, studies in RA have documented very high rates of depression in individuals with RA as compared to those without RA [24,125,126].

Third, there is a dearth of studies on newly diagnosed depression after arthritis diagnosis. This is important for comanagement of multiple conditions and treatment of newly developing conditions. There is evidence of reductions in depressive symptoms due to antirheumatic treatment. For example, depression levels decreased significantly following commencement and continuity of rituximab, a B cell-directed therapy, among individuals with RA [199]. Therefore, future studies need to systematically evaluate whether antirheumatic treatment among individuals with RA can help alleviate depressive symptoms.

Fourth, when depression burden is measured in terms of HRQoL, studies were consistent in documenting a negative relationship between the presence of depression and HRQoL [170–173]. Despite the substantial impact of depression on HRQoL, less than 15% rheumatologists collect information on patient-reported outcomes, specifically HRQoL [200]. This has implications for clinical practice because it has been reported that HRQoL is critical in assessing the treatment response for arthritis and can capture patients and other important perspectives that may not be captured by clinical assessment alone [200]. It has to be noted that most studies focused only on RA, and studies of HRQoL associated with depression among individuals with other types of arthritis such as OA, SLE were typically nonexistent.

Fifth, when the burden of depression was quantified in terms of disability, studies reported a consistent relationship between the presence of depression and disability. One study suggested that the negative impact of depression on disability was multiplicative, rather than additive [201]. However, the definitions of disability varied among studies. In this context, it has to be acknowledged there is no consensus on how to measure disability. A report by the Office of Disability, Aging and Long-Term Care Policy reviewed disability definitions in 40 different national surveys and listed at least 18 different definitions of disability that

encompassed simple general health measure to the number of physical limitations, social participation, mental and emotional symptoms [178]. The report recommended uniformly worded disability questions so that the responses can be compared across surveys and countries. Although the studies did not explicitly provide a conceptual framework for defining disability, we observed that the studies adopted a very broad definition of disability as suggested by the WHO-ICF model.

Sixth, regarding the burden of depression as measured by mortality, studies often distinguished between natural and unnatural causes of death due to the high correlation between suicide and depression [191,192]. However, most of the studies focused on RA, and we did not find any studies on the relationship between depression and mortality among individuals with OA or other forms of arthritis.

Last, we found that only two studies estimated the excess economic burden of depression among individuals with arthritis. These two studies found that among adults with arthritis, direct medical care costs were higher for those with depression compared to those without depression. One study was restricted to adults with OA and depression, and another study was restricted to adults with RA and depression. As stated in the section on costs, costs can be measured from a payer's, patient's, and societal perspective. However, we did not find any studies that focused on the financial burden on the patients and the society. Robustly designed studies to estimate excess economic burden of depression among individuals with arthritis are needed.

9. Five-year review

After reviewing currently available evidence on the burden of depression among individuals with arthritis, we propose some suggestions here for future research:

- In 2013, changes were made in defining depression. DSM-V now includes bereavement depression to be classified as the MDD [202]. This may increase the number of individuals classified as having depression and escalate the prevalence of depression among individuals with arthritis. Therefore, future studies need to incorporate the new definition of depression for prevalence and incidence estimates.
- It has to be noted that worldwide, depression is two times as likely in women as in men [203] and arthritis is more likely among women [20]; consequently, in many studies overwhelming individuals with arthritis and depression were women. In one study, 84.5% of the sample with depression and arthritis were women [74]. It is plausible that the existing tools of depression are not sensitive enough to detect depression in men [38]. Therefore, futures studies need to examine depression among men with arthritis using depression scales that are sensitive to men.
- As the studies demonstrate that depression is highly prevalent among individuals with arthritis, future studies need to evaluate whether depression is being treated among these individuals in real-world settings. Further, there is a need to assess whether depression treatment provides relief from both depressive symptoms and

arthritis-related outcomes. In this context, the Improving Mood-Promoting Access to Collaborative Treatment (IMPACT) trial suggested that collaborative care for depression can reduce depressive symptoms as well as improve arthritis-related outcomes [204]. In real-world practice settings with fee-for-service structure, implementing collaborative care may not be feasible. Therefore, policies and programs that encourage collaborative care need to be promoted.

- A significant knowledge gap exists with regard to estimation of direct medical care costs from a payer's and patient/family's perspectives. Future studies need to estimate direct healthcare costs by the payers, out-of-pocket spending by the patients and/or their families using comparison groups and indirect costs using robust statistical methods.
- As anxiety typically coexists with depression and is more prevalent than depression among individuals with RA [19,74,114], studies need to distinguish between the presence of comorbid depression and anxiety.
- As our review highlights, there are numerous studies that have documented the negative impact of depression on HRQoL among individuals with arthritis. Yet, only 15% of the rheumatologists collected information on patient-reported outcomes such as HRQoL [205] suggesting that clinical practice may not have been widely affected by the scientific evidence generated by studies. Therefore, there needs to be a concerted effort in disseminating the evidence from scientific studies through a partnership with clinicians, providers, health systems, payers, and other stakeholders.
- As there are numerous measures of disability, future studies on disability and depression among individuals with arthritis may need to adopt a uniform set of questions. There should be an internationally agreed standard method for collecting functioning information in surveys of arthritis using the ICF conceptual framework [163].

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Key issues

- Depression is highly prevalent in all forms of arthritis. However, most of the studies have focused on RA.
- Large variations in depression prevalence based on depression definition, type of arthritis, depression measurement tools, use of different thresholds with the same tools, and country of residence.
- Depression imposes a significant burden on health-related quality of life, disability, and mortality of individuals with arthritis.
- Depression can lead to higher costs; however, there are only two studies that have estimated excess direct medical care costs of depression among individuals with arthritis.
- Future studies are needed in the following areas: incident depression, robust evaluation of indirect costs, and depression-attributable healthcare utilization.
- Studies that examine depression-attributable burden in different forms of arthritis are needed.
- Future studies need to evaluate the beneficial effect of treating depression in real-world settings.

Table 1

Reported prevalence of depression among individuals with rheumatoid arthritis, osteoarthritis, and systemic lupus erythematosus.

Tools used for detecting depression	Thresholds	Prevalence (%)	References
Rheumatoid arthritis (RA)			
DSM-III	NA	23.3–27	[22,23]
DSM-IV	NA	14–41.5	[24–27]
ICD-9/10-CM	NA	7.5–66.3	[28,29]
HADS	7	15–53.2	[30,31]
	8	20–55.6	[6,32–37]
	9	23.4–55.8	[38,39]
	10	0–25.6	[32,40–42]
	11	2.9–20.6	[6,34–36,43–51]
	15	4.5	[36]
CES-D	6	22.7	[52]
	9	31.2	[53]
	10	29.8	[54]
	12	13	[55]
	15	35–37.2	[56,57]
	16	23.5–60	[58–70]
	17	20.3	[71]
	19	17.3	[59]
	23	11.7, 16	[59,72]
	27	7.4	[59,73]
BDI	10	35–63.6	[74,75]
	13	30	[76]
	16	26.5–63.3	[74,77–79]
PHQ-9	10	36–65	[80–83]
Zung SRS	40	48.9–56.2	[84,85]
	48	33.5–38	[86,87]
Osteoarthritis (OA)			
ICD-9/10-CM	NA	20.6–61.3	[88,89]
HADS	8	4.1–40.7	[90–94]
	10	5.6–8.3	[95,96]
CES-D	16	9.7–46	[97–101]
BDI	14	11.4–27	[102,103]
	16	26.3–49.3	[77,78,104]
	17	27	[105]
PHQ-9	10	14	[106]
	15	19.16–19.76	[107]
PHQ-8	10	30.5	[108]
Zung SRS	40	50.8	[109]

Tools used for detecting depression	Thresholds	Prevalence (%)	References
GDS	3	15.3–15.9	[110]
	Not reported	27.8	[111]
Systemic Lupus Erythematosus (SLE)			
DSM-IV	NA	18.75	[112]
HADS	8	23.3	[113]
	10	15	[114]
	Not reported	13–31.5	[115,116]
BDI	16	60	[117]
	18	41.7	[118]
	40	20.6	[119]
	Not reported	16.6–38.9	[115,120]
Zung SRS	40	32.9	[121]

BDI: beck's depression inventory; CES-D: the center for epidemiologic studies depression scale; DSM-III/IV: the diagnostic and statistical manual of mental disorders, third/fourth edition; GDS: the geriatric depression scale; HADS: the hospital anxiety and depression scale; ICD-9/10 CM: the international classification of diseases – 9th/10th edition medical diagnosis codes; NA: not applicable; PHQ-8: the patient health questionnaire with eight items; PHQ-9: the patient health questionnaire with nine items; Zung SRS: the zung self-rating depression scale.