AMERICAN COLLEGE
of RHEUMATOLOGY
Empowering Rheumatology Professionals

Prevalence and Risk Factors of Substance Use Disorder in Rheumatoid Arthritis

Kaarina Kowalec,[1] Heather Carney,[2] Mitulkumar Patel,[3] Carol Hitchon,[2] James M. Bolton,[2] Scott B. Patten,[3] Lesley A. Graff,[2] Charles N. Bernstein,[2] Christine Peschken,[2] Ruth Ann Marrie,[2] and for the Canadian Institutes of Health Research Team in Defining the Burden and Managing the Effects of Psychiatric Comorbidity in Chronic Immunoinflammatory Disease

Objective. In this study, we aimed to determine the lifetime prevalence of substance use disorder (SUD) in a Canadian rheumatoid arthritis (RA) cohort and factors associated with SUD in RA.

Methods. Participants with RA (N = 154) were recruited via rheumatology clinics as part of a larger cohort study of psychiatric comorbidity in immune-mediated inflammatory diseases. SUD is defined as the uncontrolled use of a substance despite the harmful consequences of its use. To identify lifetime SUD, the Structured Clinical Interview for *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* was administered to participants. Participants' sociodemographic and RA clinical characteristics were also assessed. We examined factors associated with lifetime SUD using unadjusted and adjusted logistic regression modeling.

Results. Twenty-three (14.9%) of 154 participants with RA met the criteria for a lifetime diagnosis of SUD. The majority of the participants were women, were White, had postsecondary education, and were on a disease-modifying antirheumatic drug. Factors associated with increased odds of SUD were male sex (adjusted odds ratio [aOR]: 3.63, 95% confidence interval [CI]: 1.03-12.73), younger age (aOR: 0.94, 95% CI: 0.90-0.98), and ever smoking (aOR: 6.44, 95% CI: 1.53-27.07).

Conclusion. We found that approximately 1 in 7 individuals with RA had a lifetime diagnosis of SUD, highlighting the importance of identifying and treating SUD in those with RA. In particular, the following factors were associated with higher odds of SUD: male sex, younger age, and smoking behaviors.

INTRODUCTION

Substance use disorder (SUD) is defined as the uncontrolled use of an illegal or legal substance, drug, or medication despite the harmful consequences of its use (1). SUD is associated with substantial morbidity and increased mortality. Globally, in 2016, alcohol use disorder was responsible for 16.2 million disability-adjusted life-years (DALYs), and 20.4 million DALYs were attributable to drug use disorder (2). Major depressive disorder (MDD) and anxiety disorder (AD) are well-established risk factors for SUD, and there is a known increased prevalence of MDD and AD in rheumatoid arthritis (RA), suggesting there may be a relatively high prevalence of SUD in RA (3,4).

Hospitalizations due to alcohol use disorder increased 3.5-fold between 1998 and 2014 in a US cohort of patients with RA (5), with similar increases found for other drug disorders, including cocaine, hallucinogenic drugs, amphetamine, anxiolytics, sedatives, and hypnotics (6), highlighting the potential burden of substance use in RA. Previous investigations of SUD in the general arthritis population (including RA, osteoarthritis, and rheumatism) found an increased prevalence of SUD (21.4% with osteoarthritis and RA vs 11.8% without arthritis) compared with the general population (7–9). Investigations of SUD as defined by using the gold standard assessment for mental disorders (10), the Structured Clinical Interview for *Diagnostic and Statistical Manual of Mental Disorders* (DSM) (11), exclusively in RA are limited, with one study of 200 Chinese patients with RA reporting a lifetime prevalence of alcohol use disorders and drug use disorders of 2.0% and 1.0%, respectively (12).

There is significant global variability in the prevalence of SUD (2), suggesting that prevalence of SUD in an East Asian population may differ significantly from that in a North American population. In addition, factors associated with SUD in RA are unknown. In this study, we aimed to determine the lifetime prevalence of SUD in a Canadian RA cohort and factors associated with SUD in RA.

PATIENTS AND METHODS

Study design and population. This analysis used enrollment visit data from a cohort study investigating psychiatric comorbidities in immune-mediated inflammatory disease, as described elsewhere (13). Between 2014 and 2016, participants were recruited from various sites within the Canadian province of Manitoba. To ensure representativeness, recruitment methods included general and targeted routes (including poster placement in hospitals, community primary care, rheumatology clinics, and educational institutions) and in person or mail recruitment of patients from two local rheumatology clinics. RA was confirmed by a medical records review or through the treating physician (14). Participants were aged 18 years or older, were able to provide informed consent, and had sufficient knowledge of the English language to participate in the study.

Procedures. Sociodemographic and clinical information was captured via self-report questionnaires completed during participants' initial study visits. Trained interviewers administered the Structured Clinical Interview for DSM-IV (SCID) in person or over the phone (11,13). Interviewers included nurses, graduate students, and research coordinators who were trained by a registered clinical health psychologist, as described elsewhere (13).

Measures. *Sociodemographic and clinical characteristics.* Self-report questionnaires provided the following characteristics: sex, age, household income, highest level of education attained, race, marital status, and smoking history. To ensure

reasonable cell sizes, the following were categorized: annual household income (<\$50 000, ≥\$50 000, or "decline to answer"), educational attainment (high school or below, above high school), race (White or non-White), and marital status (single: never married, divorced, widowed, separated; or married/common law). Current and past smoking behaviors were recorded, and participants who reported having smoked 100 or more cigarettes in their lifetime were categorized as ever smokers (13). Self-reported physical comorbidities that were physician diagnosed (including cardiovascular diseases, diabetes mellitus, kidney disease, and cancers, among others) were recorded by using a validated comorbidity questionnaire (15). The Modified Medical Outcomes Study Pain Effects Scale was used to record the impact of pain. This valid, reliable tool is derived from the Pain Effects Scale (16–18) and includes a six-item assessment of the effects of pain, defined as any unpleasant sensory symptom, on mood and activities during the previous 4 weeks, with scores ranging from 6 to 30 and higher scores indicating greater impact of pain.

RA-specific characteristics. Year of symptom onset and year of diagnosis were reported by participants. Current and past disease-modifying therapy (including use of any medication and use of prednisone, disease-modifying antirheumatic drugs [DMARDs], or biologics) was recorded. Disease activity was characterized by the Clinical Disease Activity Index (CDAI) (19). The CDAI score is obtained by summing disease activity according to the patient (score of 0-10) and the physician (score of 0-10) and the number of tender and swollen joints (28-joint count) (20). Scores range from 0 to 76, with scores less than or equal to 2.8 indicating remission, scores of 2.9 to 10.0 indicating low activity, scores of 10.1 to 22.0 indicating moderate activity, and scores greater than or equal to 22.1 indicating high disease activity (21). The modified Health Assessment Questionnaire (mHAQ), a self-reported measure of difficulty performing eight daily tasks, was used to characterize physical functioning (22,23). Scores for each activity (0, without difficulty; 1, with some difficulty; 2, with much difficulty; 3, unable to do) are averaged to yield a final score ranging from 0 to 3.

Mental disorders. We used the DSM-IV criteria to identify psychiatric disorders (13). The DSM-IV was the prevailing diagnostic criteria at the time the study was designed. SUD is a group of disorders defined as the uncontrolled use of an illegal or legal substance. In those with RA, SUD was defined by meeting the diagnostic criteria for current or lifetime SUD and categorized by DSM-IV diagnoses (24): alcohol abuse, alcohol dependence, drug abuse, and drug dependence. We included the following drugs in this definition: sedatives, hypnotics, stimulants, cocaine, cannabis, anxiolytics, opioids, hallucinogens, and other drugs (eg, steroids, solvents). We did not include tobacco use. We also summarized self-reported lifetime alcohol and substance use that did not meet DSM-IV diagnostic criteria, which we report here as ever substance use.

We obtained both current and lifetime rates of AD and MDD to allow for a greater understanding of the lifetime relationship between SUD and AD and/or MDD. We used the DSM-IV criteria for AD, which includes panic disorder, generalized AD, agoraphobia without history of panic disorder, specific phobia, social phobia, AD due to a general medical condition, substance-induced AD, obsessive-compulsive disorder (OCD), and posttraumatic stress disorder (PTSD). Because the DSM-5 has replaced the DSM-IV in the time since the study was designed, we repeated our analyses, characterizing current and lifetime AD in a way that more closely reflects the DSM-5 concept of an AD, which does not include OCD and PTSD.

Statistical analysis. We summarized the participant characteristics for the full RA cohort and then by the presence or absence of SUD using descriptive statistics, including mean (SD), median (interquartile range), and frequency (percentage). We

Table 1. Characteristics of those with RA and comorbid SUD

	1. All RA	2. RA/no SUD	3. RA/SUD	P
No. (%)	154 (100)	131 (85.1)	23 (14.9)	-
Male sex, n (%)	24 (15.6)	18 (13.7)	6 (26.1)	0.23
Age,[a] median (IQR), y	61.2 (52.3-67.4)	62.3 (53.8-67.9)	53.1 (46.1-60.5)	0.01*
Race, n (%)				0.14
White	116 (75.3)	102 (77.9)	14 (60.9)	-
Non-White/other	38 (24.7)	29 (22.1)	9 (39.1)	-
Income, n (%)				0.49
<$50 000	70 (45.5)	57 (43.5)	13 (56.5)	-
≥$50 000	73 (47.4)	64 (48.9)	9 (39.1)	-
Decline to answer	11 (7.2)	10 (7.6)	1 (4.4)	-
Education, n (%)				0.06
High school or below	51 (33.1)	39 (29.8)	12 (52.2)	-
Above high school	103 (66.9)	92 (70.2)	11 (47.8)	-
Marital status, n (%)				0.52
Single/divorced/separated	61 (39.6)	50 (38.2)	11 (47.8)	-
Married/common law	93 (60.4)	81 (61.8)	12 (52.2)	-
Ever smoker, n (%)	96 (62.3)	75 (57.3)	21 (91.3)	0.00*
Age at RA onset, median (IQR), y	40.0 (29-50)	41.0 (29.3-51.0)	39.0 (27.5-45.0)	0.18
Any RA medication, n (%)				
Prednisone	23 (14.9)	20 (15.3)	3 (13.0)	1.00
DMARD	130 (84.4)	109 (83.2)	21 (91.3)	0.50
Biologic	53 (34.4)	49 (37.4)	4 (17.4)	0.10
Clinical Disease Activity Index score,[a] median (IQR)	7.5 (3.2-13.3)	7.0 (3.1-12.2)	9.6 (3.8-17.3)	0.43
High activity, n (%)	17 (11.0)	14 (10.7)	3 (13.0)	0.51
Moderate activity, n (%)	30 (19.4)	23 (17.6)	7 (30.4)	-
Low activity, n (%)	62 (40.3)	55 (42.0)	7 (30.4)	-
Remission, n (%)	34 (22.1)	29 (22.1)	5 (21.7)	-
Unknown, n (%)	11 (7.1)	10 (7.6)	1 (4.4)	-
Modified Health Assessment Questionnaire score, median (IQR)	0.44 (0-0.75)	0.38 (0-0.75)	0.75 (0.06-0.94)	0.33
Mild, n (%)	139 (90.3)	118 (90.1)	21 (91.3)	1.00
Moderate-severe, n (%)	9 (5.8)	8 (6.1)	1 (4.4)	-
Unknown, n (%)	6 (3.9)	5 (3.8)	1 (4.4)	-
Pain Effects Scale score, median (IQR)	14.0 (10.3-19.8)	14.0 (10.0-19.0)	15 (12.0-21.5)	0.22
Any physical comorbidity, n (%)	131 (85.1)	114 (87.0)	17 (73.9)	0.19
Any anxiety disorder, n (%)	51 (33.1)	40 (30.5)	11 (47.8)	0.17
Panic disorder	5 (3.3)	3 (2.3)	2 (8.7)	0.34
Social phobia	26 (16.9)	18 (13.7)	8 (34.8)	0.03*
Specific phobia	16 (10.4)	13 (9.9)	3 (13.0)	0.94
Generalized anxiety disorder	13 (8.4)	9 (6.9)	4 (17.4)	0.21
Agoraphobia	5 (3.3)	3 (2.3)	2 (8.7)	0.34
Obsessive-compulsive disorder	0	0	0	N/A
Posttraumatic stress disorder	10 (6.5)	8 (6.1)	2 (8.7)	1.00
Any anxiety disorder by DSM-5, n (%)	47 (30.5)	36 (27.5)	11 (47.8)	0.09
Major depressive disorder, n (%)	58 (37.6)	44 (33.6)	14 (60.9)	0.02*

Note. Categorical values are represented as n (%), and continuous variables are represented as median (IQR). *P* values were generated by using χ² tests (categorical) and Student's *t*-tests (continuous) to compare data in column 2 (RA/no SUD) versus 3 (RA/SUD).
Abbreviations: DMARD, disease-modifying antirheumatic drug; DSM-5, *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition*; IQR, interquartile range; N/A, not applicable; RA, rheumatoid arthritis; SUD, substance use disorder.
[a] At baseline visit.
* Statistically significant findings (*P* ≤ 0.05).

used χ^2 tests and Student's t-tests to compare participants with and without SUD.

We used logistic regression models, with Firth's method to reduce the small sample bias (25), to determine the association between various patient characteristics and SUD in RA. Associations are reported as unadjusted odds ratios and adjusted odds ratios (aORs) and 95% confidence intervals (CIs). We considered the following covariates in the multivariable model: sex (female [reference] vs male), age (continuous), marital status (married/common law [reference] vs single), number of physical comorbidities (zero [reference] vs one or more), pain impact (continuous), smoking history (never [reference] vs ever), and SCID-diagnosed MDD or AD (no [reference] vs yes). These covariates were chosen on the basis of whether they either had previously established associations with SUD in general (male sex, age, marital status, physical comorbidities, and pain impact) (9,26–28) or reached a level of significance of $P \leq 0.05$ in the unadjusted analysis. We repeated the unadjusted and adjusted regression analyses using only women to assess any sex-specific effect modification.

Statistical analyses were performed using R for Statistical Computing (version 4.0.3; R Core Team) and R-Studio (version 1.2.5019). P values ≤ 0.05 were considered statistically significant.

Ethical considerations. Ethics approval was obtained from the University of Manitoba Health Research Ethics Board.

RESULTS

Overall, a majority of the participants were women, were White, had postsecondary education, and were on a DMARD. Almost half of the participants with RA met the criteria for a SCID lifetime diagnosis of an AD (47.8%), and 60.9% met the SCID criteria for a lifetime diagnosis of MDD. Twenty-three (14.9%) of 154 participants with RA met the criteria for a SCID lifetime diagnosis of

Table 2. Occurrence of SUDs and ever substance use in the study participants (N = 154)

	n (%)
Any SCID-diagnosed lifetime SUD	23 (14.9)
By disorder	
Alcohol abuse	15 (9.7)
Alcohol dependence	12 (7.8)
Drug abuse	5 (3.3)
Drug dependence	7 (4.6)
Ever substance use	16 (10.4)
Type	
Cannabis	13 (8.4)
Sedatives/hypnotics/anxiolytics	2 (1.3)
Stimulants	1 (0.6)
Opioids	0
Cocaine	4 (2.6)
Hallucinogens/PCP	1 (0.7)
Other	1 (0.7)

Abbreviations: PCP, phencyclidine; SCID, Structured Clinical Interview for *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*; SUD, substance use disorder.

an SUD (Table 1). The most common lifetime SUD diagnosis was alcohol abuse (9.7%), followed by alcohol dependence (7.8%), with drug abuse (3.3%) or dependence (4.6%) being less frequent (Table 2). Those with a lifetime SUD diagnosis were younger, had a higher rate of ever smoking, and had a higher prevalence of social phobia and MDD compared with those without an SUD (Table 1). Higher scores on the CDAI, mHAQ, and the pain impact scale were reported in those with comorbid SUD compared with those without an SUD (Table 1). In addition, a higher proportion of those with comorbid SUD had moderate to greater CDAI scores (≥10.1) compared with those without comorbid SUD; however, this difference was not significant (RA/SUD: n = 10/23 [43.4%] vs RA/no SUD: n = 37/131 [28.2%]; P = 0.51).

In the univariate regression analyses, younger age, high school education or below, ever smoker, and lifetime MDD or AD were associated with meeting criteria for a lifetime SUD (Table 3). After we adjusted for the covariates, multivariable analyses identified male sex (aOR: 3.63, 95% CI: 1.03-12.73), younger age (aOR: 0.94, 95% CI: 0.90-0.98), and ever smoking (aOR: 6.44, 95% CI: 1.53-27.07) to be significantly associated with increased odds of lifetime SUD in RA (Table 3). In the multivariable model, education and MDD or AD were no longer associated with lifetime SUD in RA. Given the high proportion of women in the sample, we repeated the regression analyses using only women, and predictors of SUD were comparable in size and direction (Supplementary Table 1).

When the classification of AD was revised to exclude OCD and PTSD, reflecting the DSM-5 classification of AD, 47 individuals with RA (30.5%) met the criteria for a lifetime diagnosis of AD (Table 1). We repeated the regression analyses using the DSM-5 definition of AD, and predictors of SUD were similar in direction and size to those predicting SUD when we applied the DSM-IV definition of AD (Supplementary Table 2).

DISCUSSION

We assessed the lifetime prevalence of SUD in a Canadian RA cohort and examined factors associated with SUD in RA. We found that 14.9% of the individuals with RA had a DSM-IV diagnosis of SUD. Prevalence of either alcohol abuse or alcohol dependence was roughly similar at 9.7% and 7.8%, respectively, with drug abuse and dependence occurring less frequently (3.3% and 4.6%, respectively). These prevalence estimates were higher compared with those in a Chinese study with a similar study design in an RA population that reported a lifetime prevalence of alcohol use disorders of 2.0% and of drug use disorders of 1.0%, although these differences may be due to alternative criteria used or cultural differences in use or reporting of use between countries (12). On the basis of a national 2012 survey, rates of lifetime alcohol or drug abuse or dependence were higher in the general Canadian population at 18.1% and 4.0%, respectively, compared with the current study in RA (29). However, these differences may, in part,

Table 3. Regression analyses of factors associated with substance use disorders (outcome) in rheumatoid arthritis

Exposures	Univariate		Multivariable	
	OR (95% CI)	*P*	OR (95% CI)	*P*
Male sex	2.28 (0.77-6.18)	0.13	3.63 (1.03-12.73)	0.04*
Age	0.95 (0.91-0.98)	0.003*	0.94 (0.90-0.98)	0.01*
Education: high school or below (vs above high school)	2.55 (1.05-6.42)	0.04*	1.80 (0.66-4.91)	0.25
Single marital status (vs married/common law)	1.48 (0.61-3.58)	0.38		
Ever smoker (vs never smoker)	6.44 (1.96-32.91)	0.001*	6.44 (1.53-27.07)	0.01*
Higher pain impact (vs lower)	1.05 (0.97-1.13)	0.21	1.03 (0.94-1.13)	0.52
One or more physical comorbidity (vs none)	0.42 (0.15-1.22)	0.11		
Major depressive or anxiety disorder	3.28 (1.30-9.22)	0.01*	2.32 (0.82-6.59)	0.11

Note. The number of individuals for both univariate (individual exposures) and multivariable (all exposures) models: N = 154.
Abbreviations: CI, confidence interval; OR, odds ratio.
* Statistically significant findings ($P \leq 0.05$).

be due to the use of a different SUD assessment in the general Canadian population, the World Health Organization Composite International Diagnostic Interview (30). Looking to other chronic immunoinflammatory conditions, such as inflammatory bowel disease, we found similar rates of alcohol abuse (9.3%) or dependence (7.3%) and drug abuse (7.3%) or dependence (3.6%) (24). In those with multiple sclerosis, rates of alcohol abuse or dependence are also reported to be similar at 6% to 14%, depending on the measurement used (31,32).

The prevalence in our RA cohort might reflect an association between increased alcohol consumption and improved RA disease activity (33,34). Individuals with RA and comorbid SUD also reported higher, albeit not significantly, CDAI scores compared with those without a SUD; however, the current study was not designed to assess further details of substance misuse, including the reasons for misuse. Comparing SUD rates between populations and attempting to determine the direction of causality between RA and SUD is of interest. However, it is important to recognize that SUDs are lifelong disorders with periods of remission and to also recognize the potential clinical implications of an SUD. For example, significant pain is a common symptom in RA, and care is needed to provide adequate pain control without worsening addiction or causing relapses in those individuals in remission from their SUD (35).

We also examined factors associated with SUD in RA and found them to be comparable with the general population. In persons with RA, we found that men, younger individuals, and smokers had a higher likelihood of having experienced an SUD. Research on factors associated with SUD in RA is limited. However, when compared with another chronic immunoinflammatory condition, inflammatory bowel disease, we found similar factors with similar effect sizes to be associated with SUD in those with RA (24). Chronic immunoinflammatory conditions, such as RA and inflammatory bowel disease, are known to have similar features, including their relapsing remitting nature, use of immunotherapies, and also high rates of comorbid psychiatric disorders (36).

Smoking is a well-known risk factor in the development of RA and contributes to several RA disease processes, including oxidative stress, inflammation, and apoptosis (37). In the current study, we found that smoking was the strongest factor associated with SUD in RA. We found that those reporting having ever smoked in their lifetime had more than six times greater odds of having an SUD compared with those who did not report this behavior. In the general population, higher rates of smoking have been associated with alcohol or drug abuse or dependence (64.9%-75.4%) compared with those with no lifetime psychiatric conditions (32.3%) (38). A possible mechanism for the association may be nicotine facilitating the release of several neurotransmitters (eg, norepinephrine, glutamate, serotonin, and others) that are also involved with SUD (39). Shared genetic variation between smoking behaviors and SUD is also a possible explanation for the increased propensity for smokers to have higher odds of SUD (40). We also considered whether other comorbid psychiatric disorders could partially explain the association between SUD and RA; however, after we adjusted for the presence of either comorbid AD or comorbid MDD in the multivariable model, smoking remained significantly associated with SUD.

A finding consistent with SUD in the general population (41) was that men with RA had higher odds of experiencing SUD compared with women (aOR: 3.63, 95% CI: 1.03-12.73). Biological factors, such as differences in substance metabolism between men and women, are believed to contribute to sex differences in the rates of SUD (41). In addition, social factors, such as higher risk-taking in men and a greater propensity for women to avoid substances that are culturally unacceptable (42), may also partly explain our finding. We did not observe effect modification by sex with respect to the other factors associated with SUD.

MDD and AD are known contributors to SUD in the general population (43). The occurrence of AD is found to worsen the prognosis for both SUD and AD (44), with possible mechanisms being shared genetic factors, self-medication of AD, and induction of AD by substance use (45–47). For comorbid MDD and SUD, similar mechanisms are postulated, including using substances to

cope with MDD symptoms and shared genetic factors between MDD and SUD (46,48). We found that the presence of MDD or AD was associated with increased odds of SUD in RA, but such effect was attenuated after we adjusted for other factors that were also associated with MDD or AD, including sex, smoking, and age, in the multivariable model.

Cannabis was the most frequently reported substance in the participants with RA. Shortly after our study was completed in 2018, Canada legalized the use of nonmedical cannabis (49), with medical cannabis available since 2001. Given the high rate of nonmedical cannabis use in this RA cohort, warranted is future research into whether nonmedical cannabis use post legalization in Canada in individuals with RA contributes to an increased risk of SUD.

In the current study, there was no report of any nonmedical opioid use. Although this could be due to a reluctance in reporting, opioids can be prescribed for the medical treatment of pain not responsive to other analgesics in RA (50); however, their use in RA has been debated in this context. Notably, patients with RA prescribed opioids were more likely to delay initiation of a DMARD (51), and opioid use was associated with delay in adequate disease control (52), suggesting that implementation of the current RA treatment recommendations may prevent the need for opioids (53).

Our study had many strengths, including that participants with RA were recruited from both community- and hospital-based clinics and were fairly representative of the RA population in general compared with other RA population-based samples (data not shown). It is noted that the present RA cohort had a higher proportion of women, a lower proportion with White ethnicity, and a higher proportion treated with DMARDs (13). Another advantage was that psychiatric disorders were diagnosed via the SCID, which is the gold standard for these conditions. On the other hand, there are alternative measures for assessing substance use, including daily or weekly drinking amounts; thus, future investigations of substance use in RA using alternative assessments are of interest. A limitation of the study includes the replacement of the DSM-IV with the DSM-5, whereby the criterion for SUD changed from substance abuse and dependence being combined to now being a single disorder, possibly affecting rates of lifetime SUD (54). However, a previous study that examined this question found only a modest increase in the SUD prevalence following the change to the DSM-5 (30). Our study was cross-sectional, which limited our ability to investigate the association between RA clinical factors and SUD over time, in addition to the mechanistic association between RA and SUD. There are other potential factors to consider in future studies of SUD in RA, including a potential interaction between worsening RA disease activity and smoking (55) and the assessment of DMARD adherence given the association between mental disorders and nonadherence (56). Future studies should also encompass assessment of the reasons for substance misuse to provide greater understanding and potential directions for interventions.

In conclusion, we found that approximately one in seven individuals with RA had a diagnosis of SUD. In addition, the following factors were associated with higher odds of SUD: male sex, younger age, and smoking behaviors; these factors are similar to those found in the general population and provide useful confirmatory guidance for clinical screening. The morbidity of SUD from the general population highlights the importance of identifying and treating SUD in those with RA.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Kowalec had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study conception and design. Kowalec, Carney, Hitchon, Patten, Graff, Peschken, Marrie.
Acquisition of data. Hitchon, Graff, Peschken, Marrie.
Analysis and interpretation of data. Kowalec, Carney, Patel, Bolton, Graff, Bernstein, Marrie.

REFERENCES

1. American Psychiatric Association. Diagnostic and statistical manual of mental disorders: DSM-5. 5th ed. Washington (DC): American Psychiatric Association; 2013.

2. GBD 2016 Alcohol and Drug Use Collaborators. The global burden of disease attributable to alcohol and drug use in 195 countries and territories, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet Psychiatry 2018;5:987–1012.

3. Sturgeon JA, Finan PH, Zautra AJ. Affective disturbance in rheumatoid arthritis: psychological and disease-related pathways. Nat Rev Rheumatol 2016;12:532–42.

4. Marrie RA, Hitchon CA, Walld R, Patten SB, Bolton JM, Sareen J, et al. Increased burden of psychiatric disorders in rheumatoid arthritis. Arthritis Care Res (Hoboken) 2018;70:970–8.

5. Singh JA. Epidemiology and outcomes of alcohol use hospitalizations in people with gout, rheumatoid arthritis, fibromyalgia, osteoarthritis, or low back pain: a national US study. J Clin Rheumatol 2021. E-pub ahead of print.

6. Singh JA. Time-trends in cocaine, hallucinogen, amphetamine, and sedative/anxiolytic/hypnotic use disorder hospitalizations in rheumatic diseases: a national time-trends study. Clin Rheumatol 2021;40:3007–14.

7. Wells KB, Golding JM, Burnam MA. Affective, substance use, and anxiety disorders in persons with arthritis, diabetes, heart disease, high blood pressure, or chronic lung conditions. Gen Hosp Psychiatry 1989;11:320–7.

8. Patten SB, Williams JV, Wang JL. Mental disorders in a population sample with musculoskeletal disorders. BMC Musculoskelet Disord 2006;7:37.

9. Wu L-T, Zhu H, Ghitza UE. Multicomorbidity of chronic diseases and substance use disorders and their association with hospitalization: results from electronic health records data. Drug Alcohol Depend 2018;192:316–23.

10. Lobbestael J, Leurgans M, Arntz A. Inter-rater reliability of the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID I) and Axis II Disorders (SCID II). Clin Psychol Psychother 2011;18:75–9.

11. Columbia University Department of Psychiatry. SCID-IV. URL: https://www.columbiapsychiatry.org/node/13821.

12. Lok EY, Mok CC, Cheng CW, Cheung EF. Prevalence and determinants of psychiatric disorders in patients with rheumatoid arthritis. Psychosomatics 2010;51:338–338.e8.

13. Marrie RA, Graff L, Walker JR, Fisk JD, Patten SB, Hitchon CA, et al. Effects of psychiatric comorbidity in immune-mediated inflammatory disease: protocol for a prospective study. JMIR Res Protoc 2018;7:e15.

14. Aletaha D, Neogi T, Silman AJ, Funovits J, Felson DT, Bingham CO III, et al. 2010 rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. Arthritis Rheum 2010;62:2569–81.

15. Horton M, Rudick RA, Hara-Cleaver C, Marrie RA. Validation of a self-report comorbidity questionnaire for multiple sclerosis. Neuroepidemiology 2010;35:83–90.

16. Ritvo PG, Fischer JS, MIller DM, Andrews H, Paty DW, LaRocca NG. Multiple sclerosis quality of life inventory: a user's manual. New York: National Multiple Sclerosis Society; 1997.

17. Ritvo P, Fischer J, Miller D, Al E. Multiple sclerosis quality of life inventory: technical supplement. New York: National Multiple Sclerosis Society; 1997.

18. Stewart AL, Ware JE Jr, editors. Measuring functioning and well-being: the medical outcomes study approach. Durham (NC): Duke University Press; 2017.

19. Anderson J, Caplan L, Yazdany J, Robbins ML, Neogi T, Michaud K, et al. Rheumatoid arthritis disease activity measures: American College of Rheumatology recommendations for use in clinical practice. Arthritis Care Res (Hoboken) 2012;64:640–7.

20. Aletaha D, Nell VP, Stamm T, Uffmann M, Pflugbeil S, Machold K, et al. Acute phase reactants add little to composite disease activity indices for rheumatoid arthritis: validation of a clinical activity score. Arthritis Res Ther 2005;7:R796–806.

21. Anderson JK, Zimmerman L, Caplan L, Michaud K. Measures of rheumatoid arthritis disease activity: Patient (PtGA) and Provider (PrGA) Global Assessment of Disease Activity, Disease Activity Score (DAS) and Disease Activity Score with 28-Joint Counts (DAS28), Simplified Disease Activity Index (SDAI), Clinical Disease Activity Index (CDAI), Patient Activity Score (PAS) and Patient Activity Score-II (PASII), Routine Assessment of Patient Index Data (RAPID), Rheumatoid Arthritis Disease Activity Index (RADAI) and Rheumatoid Arthritis Disease Activity Index-5 (RADAI-5), Chronic Arthritis Systemic Index (CASI), Patient-Based Disease Activity Score With ESR (PDAS1) and Patient-Based Disease Activity Score without ESR (PDAS2), and Mean Overall Index for Rheumatoid Arthritis (MOI-RA). Arthritis Care Res (Hoboken) 2011;63 Suppl 11:S14–36.

22. Pincus T, Summey JA, Soraci SA Jr, Wallston KA, Hummon NP. Assessment of patient satisfaction in activities of daily living using a modified stanford health assessment questionnaire. Arthritis Rheum 1983;26:1346–53.

23. Maska L, Anderson J, Michaud K. Measures of functional status and quality of life in rheumatoid arthritis: Health Assessment Questionnaire Disability Index (HAQ), Modified Health Assessment Questionnaire (MHAQ), Multidimensional Health Assessment Questionnaire (MDHAQ), Health Assessment Questionnaire II (HAQ-II), Improved Health Assessment Questionnaire (Improved HAQ), and Rheumatoid Arthritis Quality of Life (RAQoL). Arthritis Care Res (Hoboken) 2011;63 Suppl 11:S4–13.

24. Carney H, Marrie RA, Bolton JM, Patten SB, Graff LA, Bernstein CN, et al. Prevalence and risk factors of substance use sisorder in inflammatory bowel disease. Inflamm Bowel Dis 2021;27:58–64.

25. Firth D. Bias reduction of maximum likelihood estimates. Biometrika 1993;80:27–38.

26. Hasin DS, Stinson FS, Ogburn E, Grant BF. Prevalence, correlates, disability, and comorbidity of DSM-IV alcohol abuse and dependence in the United States: results from the National Epidemiologic Survey on Alcohol and Related Conditions. Arch Gen Psychiatry 2007;64:830–42.

27. Edlund MJ, Sullivan MD, Han X, Booth BM. Days with pain and substance use disorders: is there an association? Clin J Pain 2013;29:689–95.

28. Compton WM, Thomas YF, Stinson FS, Grant BF. Prevalence, correlates, disability, and comorbidity of DSM-IV drug abuse and dependence in the United States: results from the national epidemiologic survey on alcohol and related conditions. Arch Gen Psychiatry 2007;64:566–76.

29. Statistics Canada. Table 1: rates of selected mental or substance use disorders, lifetime and 12 month, Canada, household population 15 years and older, 2012. URL: https://www150.statcan.gc.ca/n1/pub/82-624-x/2013001/article/tbl/tbl1-eng.htm.

30. Peer K, Rennert L, Lynch KG, Farrer L, Gelernter J, Kranzler HR. Prevalence of DSM-IV and DSM-5 alcohol, cocaine, opioid, and cannabis use disorders in a largely substance dependent sample. Drug Alcohol Depend 2013;127:215–9.

31. Bombardier CH, Blake KD, Ehde DM, Gibbons LE, Moore D, Kraft GH. Alcohol and drug abuse among persons with multiple sclerosis. Mult Scler 2004;10:35–40.

32. Beier M, D'Orio V, Spat J, Shuman M, Foley FW. Alcohol and substance use in multiple sclerosis. J Neurol Sci 2014;338:122–7.

33. Maxwell JR, Gowers IR, Moore DJ, Wilson AG. Alcohol consumption is inversely associated with risk and severity of rheumatoid arthritis. Rheumatology (Oxford) 2010;49:2140–6.

34. Lu B, Rho YH, Cui J, Iannaccone CK, Frits ML, Karlson EW, et al. Associations of smoking and alcohol consumption with disease activity and functional status in rheumatoid arthritis. J Rheumatol 2014;41:24–30.

35. Prater CD, Zylstra RG, Miller KE. Successful pain management for the recovering addicted patient. Prim Care Companion J Clin Psychiatry 2002;4:125–31.

36. Marrie RA, Walld R, Bolton JM, Sareen J, Walker JR, Patten SB, et al. Increased incidence of psychiatric disorders in immune-mediated inflammatory disease. J Psychosom Res 2017;101:17–23.

37. Di Giuseppe D, Discacciati A, Orsini N, Wolk A. Cigarette smoking and risk of rheumatoid arthritis: a dose-response meta-analysis. Arthritis Res Ther 2014;16:R61.

38. Smith PH, Mazure CM, McKee SA. Smoking and mental illness in the U.S. population. Tob Control 2014;23:e147–53.

39. Kalman D, Morissette SB, George TP. Co-morbidity of smoking in patients with psychiatric and substance use disorders. Am J Addict 2005;14:106–123.

40. Swan GE, Carmelli D, Cardon LR. The consumption of tobacco, alcohol, and coffee in Caucasian male twins: a multivariate genetic analysis. J Subst Abuse 1996;8:19–31.

41. McHugh RK, Votaw VR, Sugarman DE, Greenfield SF. Sex and gender differences in substance use disorders. Clin Psychol Rev 2018;66:12–23.

42. Becker JB, Perry AN, Westenbroek C. Sex differences in the neural mechanisms mediating addiction: a new synthesis and hypothesis. Biol Sex Differ 2012;3:14.

43. Lai HM, Cleary M, Sitharthan T, Hunt GE. Prevalence of comorbid substance use, anxiety and mood disorders in epidemiological surveys, 1990–2014: a systematic review and meta-analysis. Drug Alcohol Depend 2015;154:1–13.

44. McHugh RK. Treatment of co-occurring anxiety disorders and substance use disorders. Harv Rev Psychiatry 2015;23:99–111.

45. Robinson J, Sareen J, Cox BJ, Bolton JM. Role of self-medication in the development of comorbid anxiety and substance use disorders: a longitudinal investigation. Arch Gen Psychiatry 2011;68:800–807.

46. Turner S, Mota N, Bolton J, Sareen J. Self-medication with alcohol or drugs for mood and anxiety disorders: a narrative review of the epidemiological literature. Depress Anxiety 2018;35:851–60.

47. Hodgson K, Almasy L, Knowles EE, Kent JW, Curran JE, Dyer TD, et al. Genome-wide significant loci for addiction and anxiety. Eur Psychiatry 2016;36:47–54.

48. Abdellaoui A, Smit DJ, van den Brink W, Denys D, Verweij KJ. Genomic relationships across psychiatric disorders including substance use disorders. Drug Alcohol Depend 2021;220:108535.

49. Cox C. The Canadian Cannabis Act legalizes and regulates recreational cannabis use in 2018. Health Policy 2018;122:205–9.

50. Whittle SL, Richards BL, Husni E, Buchbinder R. Opioid therapy for treating rheumatoid arthritis pain. Cochrane Database Syst Rev 2011:CD003113.

51. Kimsey L, Weissman JS, Patel A, Drew A, Koehlmoos T, Sparks JA. Delay in initiation of DMARD or anti-inflammatory therapy in patients newly diagnosed with rheumatoid arthritis: an analysis of United States Military Health System TRICARE beneficiaries. Semin Arthritis Rheum 2019;48:821–7.

52. Pazmino S, Boonen A, de Cock D, Stouten V, Joly J, Bertrand D, et al. Short-term glucocorticoids reduce risk of chronic NSAID and analgesic use in early methotrexate-treated rheumatoid arthritis patients with favourable prognosis: subanalysis of the CareRA randomised controlled trial. RMD Open 2021;7:e001615.

53. Pazmino S, Verschueren P, Westhovens R. Does opioid-based pharmacotherapy have a place in rheumatoid arthritis therapy? Expert Opin Pharmacother 2021. E-pub ahead of print.

54. Hasin DS, O'Brien CP, Auriacombe M, Borges G, Bucholz K, Budney A, et al. DSM-5 criteria for substance use disorders: recommendations and rationale. Am J Psychiatry 2013;170:834–51.

55. Roelsgaard IK, Ikdahl E, Rollefstad S, Wibetoe G, Esbensen BA, Kitas GD, et al. Smoking cessation is associated with lower disease activity and predicts cardiovascular risk reduction in rheumatoid arthritis patients. Rheumatology (Oxford) 2020;59:1997–2004.

56. Xia Y, Yin R, Fu T, Zhang L, Zhang Q, Guo G, et al. Treatment adherence to disease-modifying antirheumatic drugs in Chinese patients with rheumatoid arthritis. Patient Prefer Adherence 2016;10:735–42.

APPENDIX A: MEMBERS OF THE CANADIAN INSTITUTES OF HEALTH RESEARCH TEAM IN DEFINING THE BURDEN AND MANAGING THE EFFECTS OF PSYCHIATRIC COMORBIDITY IN CHRONIC IMMUNOINFLAMMATORY DISEASE

Members of the Canadian Institutes of Health Research Team in Defining the Burden and Managing the Effects of Psychiatric Comorbidity in Chronic Immunoinflammatory Disease are as follows: Ruth Ann Marrie, James M. Bolton, Jitender Sareen, Scott B. Patten, Alexander Singer, Lisa M. Lix, Carol Hitchon, Renée El-Gabalawy, Alan Katz, John D. Fisk, Charles N. Bernstein, Lesley A. Graff, Lindsay Berrigan, Christine Peschken, and James Marriott.