

Increased Burden of Psychiatric Disorders in Rheumatoid Arthritis

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Objective. We estimated the incidence and prevalence of depression, anxiety disorder, bipolar disorder, and schizophrenia in a population-based cohort with rheumatoid arthritis (RA) as compared to an age-, sex-, and geographically matched cohort without RA.

Methods. Using population-based administrative health data from Manitoba, Canada, we identified persons with incident RA between 1989 and 2012, and a cohort from the general population matched 5:1 on year of birth, sex, and region of residence. We applied validated algorithms for depression, anxiety disorder, bipolar disorder, and schizophrenia to determine the annual incidence of these conditions after the diagnosis of RA, and their lifetime and annual period prevalence. We compared findings between cohorts using negative binomial regression models.

Results. We identified 10,206 incident cases of RA and 50,960 matched individuals. After adjustment for age, sex, socioeconomic status, region of residence, number of physician visits, and year, the incidence of depression was higher in the RA cohort over the study period (incidence rate ratio [IRR] 1.46 [95% confidence interval (95% CI) 1.35–1.58]), as was the incidence of anxiety disorder (IRR 1.24 [95% CI 1.15–1.34]) and bipolar disorder (IRR 1.21 [95% CI 1.00–1.47]). The incidence of schizophrenia did not differ between groups (IRR 0.96 [95% CI 0.61–1.50]). Incidence rates of psychiatric disorders declined minimally over time. The lifetime and annual period prevalence of depression and anxiety disorder were also higher in the RA than in the matched cohort over the study period.

Conclusion. The incidence and prevalence of depression, anxiety disorder, and bipolar disorder are elevated in the RA population as compared to a matched population.

INTRODUCTION

Psychiatric comorbidity adversely affects multiple outcomes in rheumatoid arthritis (RA). Depression, when comorbid with RA, for example, is associated with an increased risk of incident myocardial infarction (1), poor

quality of life (2), and increased mortality (3). Among persons with recently diagnosed RA, psychiatric comorbidity at onset, particularly depression, is associated with greater pain and poorer functional status at onset, and a 40% reduced likelihood of clinical remission at 1 year (4). In a secondary analysis of a clinical trial,

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Research Team in Defining the Burden and Managing the Effects of Psychiatric Comorbidity in Chronic Immunoinflammatory Disease are shown in Appendix A.

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Significance & Innovations

- Rheumatoid arthritis (RA) is associated with an increased risk of multiple psychiatric disorders, including depression, anxiety disorder, and bipolar disorder.
- The risks of depression, anxiety disorder, and bipolar disorder have not changed over time, despite substantial changes in the clinical management of RA over the 20-year study period.
- Clinicians should be aware that women and those of lower socioeconomic status are at particularly increased risk of these disorders.

symptoms of depression and anxiety were associated with a reduced likelihood of RA remission (5). However, the incidence and prevalence of psychiatric disorders in RA are incompletely understood.

In a recent systematic review, estimates of the prevalence of depression ranged broadly, from 0.04–66.3% (6). Estimates of the prevalence of anxiety range from 13–70% (7–9). However, in many prior studies, estimates of the prevalence of depression or anxiety have been of low quality because these studies were not population-based, had low participation rates, and had small samples (6). Also, previous studies comparing the prevalence of depression in the RA population versus healthy controls have produced heterogeneous effect sizes, which varied depending on the methods used (10). In the RA population, age- and sex-specific estimates have rarely been reported for depression (11) or for anxiety and other psychiatric comorbidities. As a measure of risk, incidence is more useful for the investigation of disease etiology than prevalence. Nonetheless, the incidence of psychiatric comorbidity in RA, including depression, anxiety, bipolar disorder, and schizophrenia, has been reported even less often than prevalence. Further, studies have been conducted mostly outside North America, and their findings may not apply to North American populations (11–13).

An elevated risk of psychiatric comorbidity would point toward a need for additional monitoring and clinical resources. As mental health can be modified, addressing it may be an avenue for improving outcomes in RA. Moreover, if the RA population had an increased risk for multiple psychiatric disorders, this could suggest that investigating shared risk factors or shared final common pathways would be fruitful for understanding the etiology of this elevated risk. Recent genome-wide association studies suggest that some genetic loci associated with psychiatric disorders have pleiotropic effects and may be associated with depression, bipolar disorder, and schizophrenia. Some genetic loci are jointly associated with the risk of RA and other immune-mediated disorders, as well as bipolar disorder and schizophrenia (14). Shared environmental factors, such as chronic stress secondary to chronic illness, could also play a role (15–19).

We aimed to estimate the incidence and prevalence of depression, anxiety disorder, bipolar disorder, and schizophrenia in a population-based cohort with RA, and to

provide age- and sex-specific estimates. Given that the prevalence of mood and anxiety disorders has not changed over time in the general population (20,21), we also examined temporal trends in the incidence and prevalence estimates. We compared these findings in the RA population to those in a matched cohort without RA from the general population.

PATIENTS AND METHODS

Setting and data sources. This retrospective matched cohort study took place in Manitoba, a Canadian province with a population of 1.3 million. As of the 2006 census, the last full census falling in the study period, more than 80% of the Manitoba population has a high school education or better, 55.9% live in a major urban center, and 11.6% are considered low income (22,23). Nearly 10% are visible minorities, while 15.5% identify as First Nations (indigenous peoples) (24). After obtaining approval by the University of Manitoba Health Research Ethics Board and Manitoba Health Information Privacy Committee, we accessed population-based databases in the Manitoba Population Research Data Repository housed at the Manitoba Centre for Health Policy. Since health care is publicly funded in Manitoba, these administrative (health claims) databases cover more than 98% of the population. Records are linkable at the individual level using an encrypted unique personal health identification number.

The databases (and data) used included the Population Registry (dates of birth and death, dates of health care coverage, sex, and region of residence based on 6-digit postal codes); the Discharge Abstract Database (inpatient hospitalizations, including admission and discharge dates, and up to 25 diagnoses recorded using International Classification of Diseases [ICD] codes, including codes for the Clinical Modification of the Ninth Revision [ICD-9-CM] until 2004 and the Canadian version of the Tenth Revision [ICD-10-CA] thereafter); Medical Services (physician claims, including date of service and 1 ICD-9-CM physician-coded diagnosis); and the Drug Program Information Network (DPIN; all community-dispensed prescriptions, including drug name, date of dispensation, and drug identification number [DIN]). The DIN is connected to the World Health Organization's Anatomical Therapeutic Chemical Classification System. All databases covered the period from April 1, 1985, through March 31, 2012, except DPIN, which became available in 1995.

Study populations. First, we applied a validated case definition to identify all Manitoba residents with RA during the study period (see Supplementary Table 1, available on the *Arthritis Care & Research* web site at <http://onlinelibrary.wiley.com/doi/10.1002/acr.23539/abstract>) (25). This case definition has a sensitivity of 77.12% and a specificity of 90.3% as compared to physician-recorded diagnoses in a database (26,27). We restricted the analysis to incident cases of RA by excluding cases with any health claims for 5 years before the date of the first health claim for RA (index [diagnosis] date); therefore, the earliest incident cases had an index year of 1989. Second, we created a cohort without health claims for RA or related disorders, matched 5:1 on

sex, year of birth \pm 5 years, and forward sortation area (i.e., first 3 digits of postal code). As this control cohort was established as part of a larger study involving other immune-mediated diseases, individuals with health claims for inflammatory bowel disease and demyelinating disease were also excluded. Each control was assigned the index date of its matched case.

Psychiatric disorders. As described elsewhere (28), we applied validated case definitions for identifying depression, anxiety disorder, bipolar disorder, and schizophrenia (see Supplementary Table 1, available on the *Arthritis Care & Research* web site at <http://onlinelibrary.wiley.com/doi/10.1002/acr.23539/abstract>) to identify affected individuals (29,30). To estimate the incidence of these psychiatric disorders after RA diagnosis (or the index date in matched controls), the first claim for the psychiatric disorder had to occur after the index date, and had to be preceded by a 5-year period with no claims for that psychiatric disorder. This 5-year period was selected on the basis of the observations that within our cohorts, among those who met the case definition for depression, the median time between depression claims was 24.0 days (interquartile range [IQR] 36.0–121.0); the 99th percentile of the distribution for time between claims was 497 days (1.36 years). Among those who met the case definition for anxiety, the median time between anxiety claims was 31.0 days (IQR 80–534); the 99th percentile of the distribution for time between claims was 1,810 days (4.96 years). The maximum period without claims was expected to be shorter for bipolar disorder and schizophrenia. We report the incidence for the period of April 1, 1989, through March 31, 2012.

To estimate lifetime (period) prevalence, once a person met the case definition for the selected comorbidity, he or she was considered affected in all subsequent years if alive and a resident in Manitoba. However, this approach would produce estimates influenced by the duration of followup, and some individuals identified could experience remission for varying periods. Therefore, we sought to estimate the annual period prevalence of these conditions requiring ongoing care each year. Once a person met the case definition, he or she was counted as an annual prevalent case if there was ≥ 1 hospital or ≥ 2 physician claims for the disorder in that year. We have shown that when this case definition is applied in the national general population in 2012, it produces comparable prevalence estimates for depression and anxiety disorder to those obtained in the Canadian Community Health Survey–Mental Health that same year (31). Since the case definitions for depression and anxiety disorder included prescription claims, which were only available as of 1995, in models (below) we included a binary covariate indicating whether the disorder occurred before or after these data were available. We age- and sex-standardized the incidence and prevalence estimates to the 2010 Canadian population. We report average annual sex- and age-specific incidence and prevalence estimates using the age groups 18–24, 25–44, 45–64, and ≥ 65 years, consistent with those used in the Canadian Community Health Survey (32) and large enough to ensure adequate cell sizes to protect participant confidentiality.

Covariates. Covariates included sex (with male as the reference group), age (18–24 [reference group], 25–44, 45–64, and ≥ 65 years), socioeconomic status (SES) in quintiles (best quintile as reference group), region (urban or rural [reference group]), and fiscal year. We linked participants' dissemination area-level census data by postal code to determine SES as defined by the Socioeconomic Factor Index, version 2 (SEFI-2). The SEFI-2 is a factor score that incorporates information regarding average household income, percentage of single-parent households, and unemployment and high school education rates; scores < 0 indicate better SES (33). Urban regions included Winnipeg (population $> 700,000$) and Brandon (population $> 47,000$). We included fiscal year in the regression models to evaluate temporal trends. We also included the annual number of physician visits to account for possible surveillance bias due to increased health system contacts.

Analysis. We compared incidence rates and prevalence using the 2 cohorts, adjusting for potential confounders using negative binomial regression models to account for overdispersion, for which we report rate ratios (prevalence ratio [PR] and incidence rate ratio [IRR]) and 95% confidence intervals (95% CIs). These models included the log of person-years as an offset to account for variable followup, and the covariates defined above. Models of prevalence used generalized estimating equations with an exchangeable correlation structure to account for the dependence of repeated prevalence estimates within individuals. Additional adjusted models contained the 2-way interaction of cohort*year to test if temporal trends differed between the 2 cohorts. To account for potentially long periods of remission in depression and anxiety disorders, we conducted a sensitivity analysis in which we required a 10-year period before the first claim for depression or anxiety disorder without any psychiatric disorder claims. Statistical analyses were performed using SAS, version 9.4.

Table 1. Characteristics of incident RA and matched cohorts at the index date (28)*

Characteristic	Matched cohort (n = 50,960)	RA (n = 10,206)
Female	36,793 (72.2)	7,369 (72.2)
Age at diagnosis, mean \pm SD years	53.7 \pm 16.0	53.7 \pm 16.0
Followup duration from index date (years), median (IQR)	9.05 (4.33–14.9)	9.19 (4.58–14.8)
Region of residence		
Urban	29,870 (58.6)	5,981 (58.6)
Rural	21,090 (41.1)	4,225 (41.4)
SES (SEFI-2), mean \pm SD	0.080 \pm 1.0	0.054 \pm 1.03

* Values are the number (%) unless otherwise indicated. RA = rheumatoid arthritis; IQR = interquartile range; SES = socioeconomic status; SEFI-2 = Socioeconomic Factor Index, version 2.

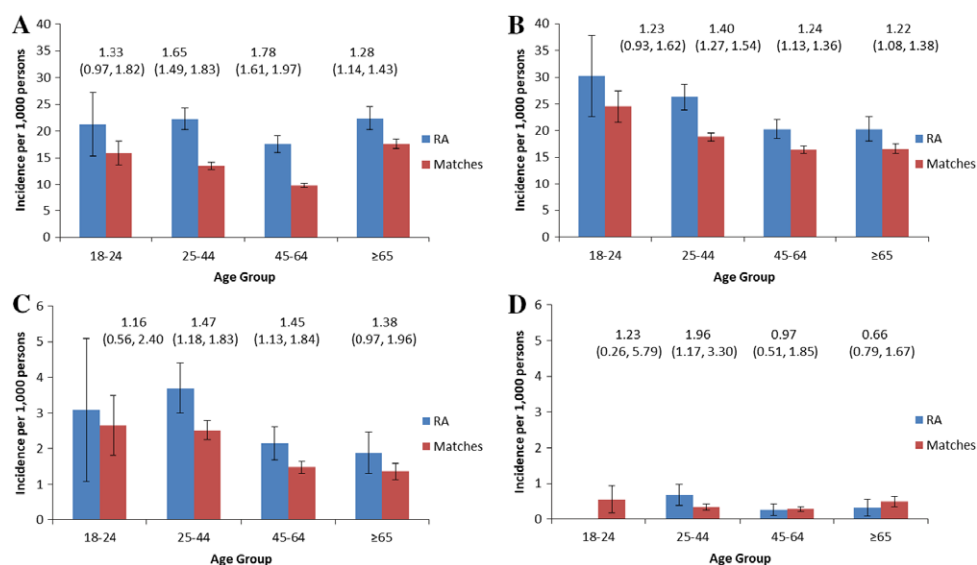


Figure 1. Age-specific average annual incidence of psychiatric disorders in the rheumatoid arthritis (RA) and matched cohorts, in **A**, depression, **B**, anxiety disorder, **C**, bipolar disorder, and **D**, schizophrenia. Incidence rate ratios (95% confidence intervals) comparing the 2 cohorts are shown at the top of each panel. Results are suppressed for schizophrenia in the 18–24 years age group in the RA cohort to preserve privacy. Color figure can be viewed in the online issue, which is available at <http://onlinelibrary.wiley.com/doi/10.1002/acr.23539/abstract>.

RESULTS

We identified 10,206 individuals with incident RA, and 50,960 matched controls. Nearly three-quarters were women, with a mean \pm SD age at the index date of 53.7 \pm 16.0 years (Table 1) (28).

Incidence. Among the psychiatric disorders, anxiety disorder had the highest annual incidence over the study period in both cohorts, while schizophrenia had the lowest incidence. In 2011, the crude annual incidence of depression per 1,000 persons in the RA cohort was 15.0 (95% CI 11.9–18.9) versus 9.09 (95% CI 8.03–10.3) in the matched cohort. In the same year, the crude annual incidence of anxiety per 1,000 persons was 16.7 (95% CI 13.2–21.2) in the RA cohort, versus 15.6 (95% CI 14.1–17.3) in the matched cohort. The average annual incidence of bipolar disorder (reported due to small cell sizes) was 2.6 per 1,000 persons (95% CI 2.3–3.0) in the RA cohort, versus 1.8 (95% CI 1.7–2.0) in the matched cohort. The average annual incidence of schizophrenia was 0.48 per 1,000 persons (95% CI 0.35–0.68) in the RA cohort, versus 0.41 (95% CI 0.34–0.50) in the matched cohort.

The average annual age-specific incidence rates of the psychiatric disorders varied by age in both cohorts (Figure 1). The incidence of depression was similar in the 18–24 and 25–44 years age groups, but declined in those ages 45–64 years before rising again (Figure 1A). The incidence of anxiety disorder declined with increasing age (Figure 1B). The incidence rate of bipolar disorder was highest among those ages 25–44 years and lowest among those age \geq 65 years (Figure 1C). In the RA cohort, the average annual age-specific incidence rate of schizophrenia was highest in those ages 25–44 years (Figure 1C). The incidence of schizophrenia was higher in the RA cohort than in the matched cohort among those ages 25–44 years, but incidence rates did not differ between cohorts for the other age groups.

The average annual incidence rates of depression, anxiety disorder, and bipolar disorder were higher in women than in men (see Supplementary Table 2, available on the *Arthritis Care & Research* web site at <http://onlinelibrary.wiley.com/doi/10.1002/acr.23539/abstract>). Within sex strata, the incidence of depression, anxiety disorder, and bipolar disorder was higher in the RA cohort than in the matched cohort; the incidence of schizophrenia did not differ between cohorts. As compared to the matched cohort, the age- and

Table 2. Comparison of age- and sex-standardized incidence and prevalence of psychiatric disorders between rheumatoid arthritis and matched cohorts in 2011*

	Incidence	Lifetime prevalence	Annual period prevalence
Depression	1.71 (1.15–2.55)	1.48 (1.35–1.64)	1.66 (1.36–2.02)
Anxiety disorder	1.21 (0.82–1.79)	1.25 (1.13–1.37)	1.63 (1.22–2.19)
Bipolar disorder	1.30 (0.63–2.68)	1.30 (1.10–1.53)	1.19 (0.80–1.78)
Schizophrenia	0.97 (0.62–1.52)†	1.10 (0.71–1.70)	0.71 (0.41–1.26)

* Values are the rate ratios (95% confidence intervals).

† Average annual incidence over study period due to small cell sizes in a single year.

sex-standardized incidence in 2011 of depression was higher in the RA cohort (Table 2). The standardized incidence of anxiety disorder and bipolar disorder were not statistically significantly higher in the RA cohort. The average annual incidence of schizophrenia did not differ between groups.

After adjustment for age, sex, area-level SES, region of residence, number of physician visits, and year, we found that the incidence of depression was higher in the RA cohort over the entire study period (IRR 1.46 [95% CI 1.35–1.58]), as were the incidences of anxiety disorder (IRR 1.24 [95% CI 1.15–1.34]) and bipolar disorder (IRR 1.21 [95% CI 1.00–1.47]) (Table 3). The incidence of schizophrenia did not differ between groups (IRR 0.96 [95% CI 0.61–1.50]).

In adjusted models, women, those of lower area-level SES, and those living in urban settings had an increased incidence of depression, anxiety disorder, bipolar disorder, and schizophrenia (Table 3). As compared to participants ages 18–24 years, those ages 25–64 years had a reduced incidence of depression, anxiety disorder, and schizophrenia. Participants ages 65 years and older also had a reduced incidence of anxiety disorder and bipolar disorder. The incidence of depression declined minimally but statistically significantly over time in both populations, while the incidence of the other disorders did not change.

Findings for depression and anxiety disorder were similar when we required a 10-year period without a diagnosis code for a psychiatric disorder before the first diagnosis code for depression or anxiety disorder, although confidence intervals for point estimates were broader (for cohort characteristics, see Supplementary Table 3, available on the *Arthritis Care & Research* web site at <http://onlinelibrary.wiley.com/doi/10.1002/acr.23539/abstract>).

Care & Research web site at <http://onlinelibrary.wiley.com/doi/10.1002/acr.23539/abstract>). Specifically, in 2011 the crude annual incidence of depression per 1,000 persons in the RA cohort was 15.1 (95% CI 11.6–19.6) versus 9.42 (95% CI 8.17–10.9) in the matched cohort. In the same year, the crude annual incidence of anxiety per 1,000 persons was 16.6 (95% CI 12.6–21.8) in the RA cohort, versus 16.3 (95% CI 14.5–18.3) in the matched cohort. After adjustment for age, sex, area-level SES, region of residence, number of physician visits, and year, the incidence of depression was found to be higher in the RA cohort over the entire study period (IRR 1.43 [95% CI 1.29–1.59]), as was the incidence of anxiety disorder (IRR 1.26 [95% CI 1.14–1.39]).

Prevalence. Among the psychiatric disorders, anxiety disorder had the highest observed lifetime and annual period prevalence, while schizophrenia had the lowest in both cohorts. Crude prevalence estimates for 2011 are shown in Figure 2. In both cohorts, participants ages 25–44 years had the highest prevalence (current and lifetime) of depression and anxiety disorder, while participants ages 25–64 years shared the highest prevalence of bipolar disorder and schizophrenia (Figure 3). The annual period and lifetime prevalence of depression, anxiety disorder, and bipolar disorder were higher for women than men in both cohorts (see Supplementary Table 4, available on the *Arthritis Care & Research* web site at <http://onlinelibrary.wiley.com/doi/10.1002/acr.23539/abstract>).

As compared to the matched cohort, the age- and sex-standardized lifetime prevalence (in 2011) of depression, anxiety disorder, and bipolar disorder were higher in the

Table 3. Association between RA and incidence of psychiatric disorders*

Variable	Depression	Anxiety disorder	Bipolar disorder	Schizophrenia
Cohort				
Matches	1.0	1.0	1.0	1.0
RA	1.46 (1.35–1.58)†	1.24 (1.15–1.34)†	1.21 (1.00–1.47)‡	0.96 (0.61–1.50)
Sex				
Male	1.0	1.0	1.0	1.0
Female	1.60 (1.48–1.73)†	1.54 (1.43–1.66)†	1.81 (1.47–2.22)†	1.77 (1.12–2.81)†
Age, years				
18–24	1.0	1.0	1.0	1.0
25–44	0.93 (0.80–1.08)	0.80 (0.70–0.91)†	1.15 (0.81–1.62)	0.90 (0.42–1.92)
45–64	0.73 (0.62–0.85)†	0.68 (0.59–0.79)†	0.76 (0.52–1.12)	0.66 (0.29–1.54)
≥65	1.16 (0.99–1.36)	0.69 (0.60–0.80)†	0.64 (0.43–0.93)†	1.12 (0.50–2.47)
Socioeconomic status				
Quintile 1 (lowest)	1.10 (1.00–1.20)†	1.16 (1.06–1.25)†	1.20 (0.97–1.49)	2.79 (1.67–4.66)†
Quintile 2	1.25 (1.15–1.37)†	1.17 (1.07–1.27)†	1.38 (1.12–1.72)†	1.49 (0.85–2.64)
Quintile 3	1.13 (1.03–1.24)†	1.12 (1.03–1.22)†	1.12 (0.90–1.41)	1.54 (0.87–2.72)
Quintile 4	1.13 (1.04–1.24)†	1.14 (1.05–1.24)†	1.17 (0.94–1.46)	1.42 (0.80–2.53)
Quintile 5 (highest)	1.0	1.0	1.0	1.0
Region				
Rural	1.0	1.0	1.0	1.0
Urban	1.13 (1.06–1.19)†	1.27 (1.20–1.34)†	1.86 (1.60–2.15)†	1.66 (1.21–2.29)†
No. physician visits	1.00 (1.00–1.00)†	1.00 (1.00–1.00)†	1.00 (1.00–1.00)†	1.00 (1.00–1.00)†
Year§	0.991 (0.984–0.997)†	1.000 (0.993–1.006)	0.997 (0.980–1.014)	0.989 (0.950–1.028)

* Values are the adjusted rate ratios (95% confidence intervals) unless otherwise indicated. Models for depression and anxiety disorders also include term to adjust for whether prescription claims were used in the case definition. RA = rheumatoid arthritis.

† Statistically significant.

‡ Statistically significant at $P = 0.05$.

§ Refers to annual change.

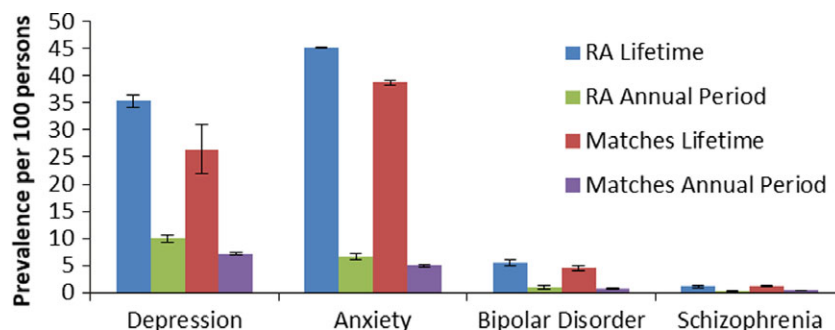


Figure 2. Crude lifetime and annual period prevalence (95% confidence intervals) of psychiatric disorders in the rheumatoid arthritis (RA) and matched cohorts in 2011.

RA cohort (Table 2). The lifetime prevalence of schizophrenia did not differ between groups (PR 1.10 [95% CI 0.71–1.70]). Similarly, the annual period prevalence of depression and anxiety disorder were higher in the RA cohort (Table 2). The annual period prevalence of bipolar disorder and schizophrenia did not differ between the 2 cohorts.

After adjustment for age, sex, area-level SES, region of residence, and year, the lifetime prevalence of depression (PR 1.35 [95% CI 1.26–1.45]) and anxiety disorder (PR 1.20 [95% CI 1.13–1.27]) were higher in the RA cohort than in the matched cohort over the entire study period (see Supplementary Table 5, available on the *Arthritis Care & Research* web site at <http://onlinelibrary.wiley.com/doi/10.1002/acr.23539/abstract>). The lifetime prevalence of bipolar disorder (PR 1.13 [95% CI 0.95–1.36]) and schizophrenia did not differ between the RA and matched cohorts (PR 1.02 [95% CI 0.72–1.43]). Similarly, after adjustment, the annual period prevalence of depression (PR 1.36 [95% CI 1.26–1.47]), anxiety disorder (PR 1.30 [95% CI 1.19–1.41]), and bipolar disorder were higher in

the RA cohort than the matched cohort over the study period (see Supplementary Table 6, available on the *Arthritis Care & Research* web site at <http://onlinelibrary.wiley.com/doi/10.1002/acr.23539/abstract>). The annual period prevalence of bipolar disorder (PR 1.06 [95% CI 0.86–1.31]) and schizophrenia did not differ between the RA and matched cohorts (PR 0.68 [95% CI 0.40–1.15]).

DISCUSSION

We conducted a large, population-based study and found that incidence and prevalence of multiple psychiatric disorders, including depression, anxiety, and bipolar disorder, were higher in the RA population than in the matched cohort from the general population. For depression and anxiety disorders, the relative increase in annual period prevalence in the RA population was higher than the relative increase in lifetime prevalence. This suggests that differences between the RA and matched populations may diminish over a lifetime as these conditions accumulate in the

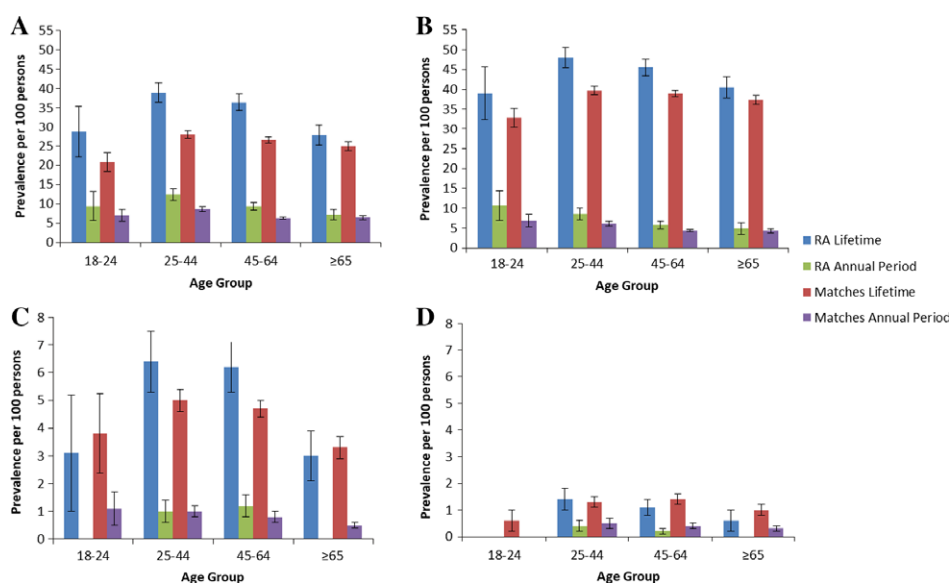


Figure 3. Age-specific lifetime and annual period prevalence (95% confidence intervals) of psychiatric disorders in the rheumatoid arthritis (RA) and matched cohorts in 2011, in **A**, depression, **B**, anxiety disorder, **C**, bipolar disorder, and **D**, schizophrenia. Results are suppressed for schizophrenia and bipolar disorder in the 18–24 years age group in the RA cohort to preserve privacy.

general population. We reported age- and sex-specific estimates, which illustrate the variation in the incidence and prevalence of these conditions across demographic groups; prior research regarding this variation is limited (11).

Similar to our study, 2 previous studies in Taiwan reported an increased incidence of depression in the RA population as compared to controls (13,34). Although the prevalence of anxiety disorders is reportedly increased in RA (7), we could not identify prior studies reporting the incidence of anxiety disorders. Our findings regarding the increased incidence of bipolar disorder in RA are consistent with 1 previous study which evaluated the association of RA and bipolar disorder (12,35,36). In that study of 2,570 individuals with RA from Taiwan and 2,570 individuals without RA, matched on age, sex, comorbidities, and date of enrollment in the national health insurance plan, RA was associated with a 2-fold increased incidence of bipolar disorder (12). Two other studies failed to show associations between RA and bipolar disorder (35,36). These differences may reflect differences in study design or study populations. We did not identify an association between RA and schizophrenia in our population, possibly due to the relatively small number of affected individuals, but the preponderance of prior studies suggests that schizophrenia occurs less often than expected in RA (37).

For both cohorts, the incidence of depression, anxiety disorder, bipolar disorder, and schizophrenia did not change meaningfully over the more than 20-year study period, while the prevalence rose minimally. We were unable to identify any comparable studies examining temporal trends in the incidence of these disorders in RA. Evaluation of changes in the prevalence of mood and anxiety disorders over time in the general population has suggested that, although access to treatment has improved, the prevalence of these disorders has not decreased (38).

Several demographic factors were found to be associated with the risk of psychiatric disorders. The peak incidence of the psychiatric disorders studied was generally among those ages 18–44 years, and declined at older ages, which is in keeping with the typical age of onset of these disorders. The incidence and prevalence of depression, anxiety, and bipolar disorder was increased in women. In the general population, female sex is associated with an increased prevalence of depression and anxiety globally (39). Prior studies in RA have also found that female sex is associated with an increased incidence of depression (11,13), although this has not always been found (8). Bipolar I disorder does not demonstrate a sex predilection, but bipolar II disorder may affect women more often than men (40). Therefore, our findings raise the possibility that bipolar II disorder may be more common in RA than bipolar I disorder. However, we could not distinguish bipolar I from bipolar II disorder using administrative data. A previous meta-analysis reported an increased prevalence of several psychiatric disorders among members of the general population living in urban areas (41). Consistent with that observation, urban residence was associated with an increased incidence of all the psychiatric disorders studied. Previously it has been proposed that, due to the presence of greater psychosocial and environmental stressors, the urban environment may contribute to the risk of disorders such as schizophrenia in genetically

susceptible individuals (42). Similarly, lower SES was associated with an increased incidence of all the psychiatric disorders, consistent with prior findings in RA (8).

Strengths of this study include the large study population and the use of population-based data sources. However, limitations should be considered. Although we evaluated multiple psychiatric disorders, we did not evaluate psychiatric multimorbidity, a common and clinically relevant issue which may affect outcomes (43,44), nor did we evaluate medical comorbidity. Because physician claims in Manitoba include only a single diagnosis, administrative data are not ideal to evaluate this issue, which deserves future study. We used administrative data, which may limit the accuracy of the diagnostic codes reported. However, we employed a validated case definition for RA that was highly specific. The sensitivity of this definition is 77%, and therefore some cases were likely missed, but this would bias findings toward the null. The case definitions used to identify psychiatric comorbidity have not been validated in RA, but they have been validated in 2 other immune-mediated inflammatory diseases and demonstrated stable performance characteristics across diseases (29,30).

Moreover, we identified the expected demographic relationships with the psychiatric disorders studied. Administrative data only identify health conditions for which individuals seek medical treatment (45) and will not identify care provided by nonphysician providers such as psychologists. Conditions that cause symptoms but do not meet diagnostic criteria may not be captured. Also, underdiagnosis of psychiatric disorders in the general and RA populations is recognized (46). All of these factors may have led to underestimation of the incidence and prevalence of psychiatric disorders, but this is unlikely to affect the relative risk of psychiatric comorbidity between cohorts. Because psychiatric disorders may be lifelong, recurrent conditions, the use of only a 5-year period of no claims may have misclassified some prevalent cases as incident, rather than recurrent, particularly for depression and anxiety disorders. This would tend to overestimate incidence rates, but would be unlikely to affect comparisons between cohorts. However, the median time between claims, of 24–31 days, and the consistency of our findings with the longer 10-year run-in period in the complementary analysis suggest that the effects of any such misclassification are likely to be small. As administrative data lack clinical details, we could not evaluate the associations between characteristics of RA or its treatments and the risk of psychiatric comorbidity. Future studies should explore these issues in population-based clinical cohorts that comprehensively evaluate multiple psychiatric disorders. Finally, the generalizability of the findings should be considered. We conducted this study in Manitoba, the Canadian province with the highest proportion of First Nations Canadians, a group at increased risk of RA. However, access to health care is similar to that in other Canadian provinces, as is educational attainment. Educational attainment is slightly higher in Canada than the Organization for Economic Cooperation and Development average (22).

We observed that RA is associated with an increased risk of multiple psychiatric disorders, including depression, anxiety disorder, and bipolar disorder, and that these risks

have not changed over time, despite changes in the clinical management of RA over the 20-year study period. Clinicians should be aware that women and those of lower SES are at particularly increased risk of these disorders.

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 submitted for publication. Dr. Marrie 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. Marrie, Hitchon, Patten, Sareen, Walker, Lix, El-Gabalawy, Katz, Fisk, Bernstein.

Acquisition of data. Marrie, Singer, Katz, Bernstein.

Analysis and interpretation of data. Marrie, Hitchon, Walld, Patten, Bolton, Walker, Singer, Lix, El-Gabalawy, Katz, Bernstein.

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

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