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Psychiatric comorbidity increases mortality in immune-mediated inflammatory diseases

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ABSTRACT

Objective: We determined the association between any common mental disorder (CMD: depression, anxiety disorder, bipolar disorder) and mortality and suicide in three immune-mediated inflammatory diseases (IMID), inflammatory bowel disease (IBD), multiple sclerosis (MS) and rheumatoid arthritis (RA), versus age-, sex- and geographically-matched controls.

Methods: Using administrative data, we identified 28,384 IMID cases (IBD: 8695; MS: 5496; RA: 14,503) and 141,672 matched controls. We determined annual rates of mortality, suicide and suicide attempts. We evaluated the association of any CMD with all-cause mortality and suicide using multivariable Cox regression models.

Results: In the IMID cohort, any CMD was associated with increased mortality. We observed a greater than additive interaction between depression and IMID status (attributable proportion 5.2%), but a less than additive interaction with anxiety (attributable proportion −13%). Findings were similar for MS and RA. In IBD, a less than additive interaction existed with depression and anxiety on mortality risk. The IMID cohort with any CMD had an increased suicide risk versus the matched cohort without CMD.

Conclusion: CMD are associated with increased mortality and suicide risk in IMID. In MS and RA, the effects of depression on mortality risk are greater than associations of these IMID and depression alone.

1. Introduction

Survival is lower than in age and sex-matched healthy populations for immune-mediated inflammatory diseases (IMID), including inflammatory bowel disease (IBD) [1], multiple sclerosis (MS) [2–4] and rheumatoid arthritis (RA) [5], which share features of inflammation and immune dysregulation. Although disease-specific factors contribute to reduced survival in IMID, findings in other diseases suggest that psychiatric comorbidity may exacerbate mortality risk [6]. Psychiatric comorbidities, including depression, anxiety disorders and bipolar disorder, are common in IMID [7], but relatively little is known about their effects on mortality. Depression is reportedly associated with increased mortality in prevalent cohorts with RA and MS [8–10], but the effects of depression on IBD are unknown, and the effects of depression on mortality may differ across diseases. Moreover, although anxiety disorders and bipolar disorder occur more often in IMID than in the general population, their effects on mortality have received little attention. This is particularly concerning for anxiety given the conflicting literature regarding the association between anxiety disorders and mortality in the general population [11, 12]. Finally, it is unknown whether the joint effects of psychiatric comorbidity and IMID are additive, less than additive or greater than additive; greater than additive (i.e. synergistic)

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effects would have important clinical implications and suggest the need for causal research to explain the underlying biologic interaction.

Suicide may occur with increased frequency in IMID, but the findings are inconsistent, and it is uncertain if the risk of suicide is fully accounted for by comorbidity [13]. In IBD, studies variously suggest that the risk of suicide is increased, decreased or unchanged [14, 15]. In MS, one meta-analysis reported that the risk of suicide is increased, but more recent studies suggest that this is no longer true [16, 17]. Even less is known about suicide attempts [15, 18], which identify individuals at high risk of suicide.

If the effects of psychiatric comorbidity on mortality are generally consistent across IBD, MS and RA, this would suggest that the effects may be generalizable to other IMID. We aimed to determine how psychiatric disorders were associated with survival in three IMID (IBD, MS and RA) compared to unaffected controls, and whether the joint effects of the IMID and psychiatric disorders produced greater than additive effects on survival.

2. Methods

2.1. Setting and data sources

Manitoba is a central Canadian province. Health care is universal and publicly funded. Electronic records of health service delivery are prospectively captured in administrative databases. We accessed databases housed at the Manitoba Population Data Repository at the Manitoba Centre for Health Policy, including the population registry, discharge abstract database, physician claims, and the Drug Program Information Network (DPIN). The Population registry includes dates of birth and death, sex, dates of health care coverage, and region of residence (postal code) for each resident. The discharge abstract database captures all hospitalizations, including dates of admission and discharge and up to 25 diagnoses are using International Classification of Disease (ICD) codes. These diagnoses were recorded using (ICD), 9th revision, Clinical Modification (ICD-9-CM) codes up to 2004, and using ICD 10th revision, Canadian version (ICD-10-CA) codes thereafter. Physician claims capture the date of service, type of service, and one ICD-9-CM coded diagnosis. Outpatient prescription dispensations are recorded by the DPIN, including date of dispensation, drug name, and drug identification number (DIN), which is linked to the World Health Organization's Anatomical Therapeutic Chemical (ATC) Classification System. DPIN records covered the period April 1, 1995-March 31, 2013. All other databases covered the period April 1, 1984-March 31, 2013; this latter period constituted the study period for this analysis. To preserve confidentiality the databases were deterministically linked at the individual level using an encrypted unique identifier.

We linked these databases to the Manitoba Vital Statistics Death Database which captures all deaths in Manitoba, including date and cause of death [19]. From 1979 to 1999, the vital statistics database used ICD-9 coding and ICD-10-CA coding thereafter. Until 1999 one cause of death was available, but since 2000 the primary cause of death and ≤ 20 contributing causes of death have been available.

The University of Manitoba Health Research Ethics Board approved this study and the Manitoba Health Information Privacy Committee approved access to health databases. The Vital Statistics Agency approved access to the Vital Statistics Death Database.

2.2. Study populations

As described previously [7], we applied validated case definitions (Table e1) to our linked administrative databases to identify Manitobans with IBD, MS and RA [20–22]. We defined the date of diagnosis (index date) as the date of the first health claim for the IMID of interest during the study period. Next, we selected general population cohorts which were individually matched 5:1 on sex, year of birth within ± 5 years, and forward sortation area (i.e. first 3 digits of postal code) to the IMID cohorts. Statistical efficiency is optimized at 4–6 controls. Potential controls with any diagnosis codes for IBD, demyelinating disease, RA and related disorders were excluded as were individuals receiving MS-specific disease-modifying therapies that constituted part of the MS case definition [21]. We assigned each control the index date of its matched case.

2.3. Psychiatric disorders (exposure)

The exposure of interest was psychiatric comorbidity, including depression, anxiety and/or bipolar disorder. We chose these disorders because of their increased incidence in IBD, MS and RA [7], they are the most common psychiatric disorders in the general population, are sufficiently common in IMID to facilitate multivariable analysis, and validated case definitions for them exist in MS and IBD populations (Table e1) [23, 24]. We applied case definitions for depression, anxiety and bipolar disorder and any common mental disorder (CMD, defined herein as, ≥ 1 of depression, anxiety disorders, bipolar disorders) to the study cohorts to identify affected individuals. We considered individuals affected by each disorder to be affected from the date of the first health claim for that disorder (diagnosis date).

2.4. Outcomes

The primary outcome of interest was all-cause mortality. The secondary outcome was death due to suicide. We also report suicide attempts. Cause of death was identified using the vital statistics database. Suicide was defined by diagnostic codes for accidental poisoning, self-inflicted poisoning, and self-inflicted injury (ICD-9-CM E950-E959, E980-989, E850-E854, E858, E862; ICD-10-CA X60–84, Y10–Y34, X40–X42, X46, X47) [25, 26]. Suicide attempts were identified by hospital admissions and physician claims with the aforementioned diagnosis codes.

2.5. Covariates

Covariates in the regression analyses, described below, included sex (male as reference group), age at the IMID index date (18–24 [reference group], 25–44, 45–64, ≥ 65), birth year (< 1934 [reference group], 1934–1949, 1950–1961, 1962–1994), socioeconomic status (SES) in quintiles (lowest quintile of SES as reference group), region (urban or rural [reference group]), and physical comorbidities. We linked postal codes to census data to determine SES at the index date. Specifically, we determined SES using the Socioeconomic Factor Index version 2 (SEFI-2) which incorporates information regarding average household income, percent of single parent households, unemployment rate and high school education rate based on dissemination area level census data; scores < 0 indicate higher SES [27]. Urban regions included the cities of Winnipeg (population $> 600{,}000$) and Brandon (population $> 47{,}000$). The physical comorbidities assessed included hypertension, diabetes, ischemic heart disease, psoriasis, chronic lung disease and cancer. The cancer variable included the presence of any of the four most common cancers (breast, lung, colorectal, prostate). We selected these comorbidities based on their associations with psychiatric disorders in MS, RA or the general population [28–30], the availability of validated administrative definitions (Table e-1) [31–34], their reported associations with mortality in ≥ 1 of the IMID populations of interest, or their recognition as one of the leading causes of death in Canada. All of these comorbidities were chronic conditions, therefore, once an individual met the case definition for a condition, he or she was considered affected thereafter if still alive and living in Manitoba. Since some of the case definitions for psychiatric disorders included prescription claims, which were only available as of 1995, we included a binary model covariate indicating whether the disorder occurred before or after the availability of these data.

2.6. Analysis

We report average annual age and sex-specific all-cause mortality rates for each cohort, and all-cause mortality rates which were age- and sex-standardized to the 2010 census population. We also report rates of death by suicide, and suicide attempts. Initially, we compared survival from birth (lifespan) between the cohorts using a univariate Cox proportional hazards model with age as the time scale, since age is the strongest predictor of mortality [35]. We accounted for left truncation of the data using age at entry into the study given that data were available from 1984 onward [36, 37]. Second, we constructed a multivariable Cox model to evaluate the association of psychiatric disorders with survival, adjusting for covariates as defined above. To evaluate the individual and joint effects of any CMD and IMID on mortality, we created four groups where R = relative hazard/risk: (i) no IMID and no psychiatric comorbidity (reference group [R_{00}]); (ii) with IMID but no CMD [R_{10}]; (iii) with any CMD but no IMID [R_{01}]; and (iv) with IMID and any CMD [R_{11}]. To assess a possible biological interaction of psychiatric comorbidity and IMID on mortality using a departure from additivity effects [38], we calculated the relative excess risk of interaction (RERI) as $R_{11} - R_{01} - R_{10} + 1$ [39, 40]. We also calculated the attributable proportion (AP) due to interaction along with 95% confidence intervals (95%CI) [39]. Third, we constructed multivariable Cox regression models to examine the association of individual psychiatric comorbidities (depression, anxiety, bipolar disorder) with survival with IMID generally (IBD, MS and RA as a group), then stratified by specific IMID. Finally, we used the same approach to examine the association of psychiatric comorbidity with mortality due to suicide, except that we also accounted for the competing risk of death due to other causes using a cause-specific hazard function [41].

We evaluated model fit using the likelihood ratio test, and assessed the proportionality assumption using descriptive statistics and plots of the survival function. To address departures from proportionality, SES was included as a time-dependent covariate in all models. Birth year was included as a stratifying variable in the all-cause mortality models.

Statistical analyses were performed using SAS V9.4 (SAS Institute Inc., Cary, NC).

3. Results

3.1. Participants

We identified 28,384 IMID cases including 8695 with IBD, 5496 with MS, and 14,503 with RA (Table 1). Combined, the matched cohorts included 141,672 matched controls. Two-thirds of the IMID cohort were female; the cohort's mean (SD) age was 47.9 (17.1) years. One-quarter of the IMID cohort had any CMD (n = 7116) at the index date, a proportion 4.5% higher than in the matched cohort.

3.2. Mortality in the IMID cohort

Median survival in the IMID cohort from birth was 83.4 (95% CI: 83.1, 83.7) years, whereas it was 86.1 (95% CI: 86.0, 86.2) years in the matched cohort ($p < 0.0001$). In 2012, the standardized mortality rate in the IMID cohort was 14.7 per 1000 (95% CI: 13.2, 16.3), higher than in the IMID matched cohort (9.84 per 1000; 95% CI: 9.30, 10.4; rate ratio [RR] 1.49; 95% CI: 1.32, 1.68).

After adjustment, the IMID cohort had an increased risk of death versus the matched cohort without any CMD, whether or not any CMD was present in the IMID cohort. The presence of any CMD was associated with increased mortality in the IMID and matched cohorts, but we did not observe an additive interaction (Table 2). However, we observed an additive interaction between depression and IMID status (Table 2); 5.2% of the increased mortality in the IMID cohort was due to the joint effects of having an IMID and depression. By contrast, we observed a less than additive interaction between anxiety and IMID status such that mortality was lower among participants with an anxiety disorder and an IMID than participants with an IMID who did not have an anxiety disorder. Bipolar disorder was associated with increased mortality in the IMID and matched cohorts, but we did not observe an interaction.

3.3. Suicide in the IMID cohort

Overall, crude average annual suicide rates (per 100,000) did not differ between the IMID and matched cohorts (Table 3). After stratification, suicide rates were higher in the IMID cohort than in the matched

Table 1
Characteristics of prevalent disease cohorts and matched cohorts.

Characteristic	IBD matched (n = 43,465)	IBD (n = 8695)	MS matched (n = 27,354)	MS (n = 5496)	RA matched (n = 72,396)	RA (n = 14,503)
Female, n (%)	23,743 (54.5)	4751 (54.5)	19,465 (70.8)	3905 (70.7)	52,969 (72.6)	10,555 (72.6)
Age at diagnosis, mean (SD)	41.2 (16.7)	41.2 (16.8)	42.1 (13.4)	42.1 (13.4)	54.2 (16.1)	54.2 (16.1)
Duration of follow-up (years), median (IQR)	12.2 (5.3–20.8)	12.6 (5.8–21.1)	13.4 (6.4–22.6)	12.8 (6.09–20.8)	10.9 (5.1–18.5)	10.8 (5.3–17.7)
Region of residence, n (%)						
Urban	29,352 (67.4)	5874 (67.4)	18,653 (67.9)	3752 (68.0)	42,944 (59.2)	8602 (59.2)
Rural	14,183 (32.6)	2839 (32.6)	8828 (32.1)	1768 (32.0)	29,648 (40.8)	5939 (40.8)
Socioeconomic status (SEFI-2)	−0.23 (0.90)	−0.27 (0.92)	−0.21 (0.90)	−0.26 (0.92)	0.05 (1.00)	0.03 (1.04)
Comorbidity status at disease index date						
Any common mental disorder, n (%)	7852 (18.0)	1907 (21.9)	5306 (19.3)	1520 (27.5)	16,478 (22.7)	3827 (26.3)
Depression, n (%)	4319 (9.9)	1200 (13.8)	3035 (11.0)	968 (17.5)	9399 (13.0)	2333 (16.0)
Anxiety disorder, n (%)	6662 (15.3)	1619 (18.6)	4419 (16.1)	1251 (22.7)	13,990 (19.3)	3298 (22.7)
Bipolar disorder, n (%)	695 (1.6)	200 (2.3)	493 (1.8)	142 (2.6)	1457 (2.0)	326 (2.2)
Diabetes, n (%)	1815 (4.2)	350 (4.0)	911 (3.3)	158 (2.9)	5770 (8.0)	1131 (7.8)
Hypertension, n (%)	6025 (13.8)	1160 (13.3)	2963 (10.8)	581 (10.5)	17,814 (24.5)	3500 (24.1)
Chronic lung disease, n (%)	4633 (10.6)	1174 (13.5)	2526 (9.2)	548 (9.9)	8625 (11.9)	2367 (16.3)
Ischemic heart disease, n (%)	2062 (4.7)	488 (5.6)	720 (2.6)	146 (2.6)	6773 (9.3)	1515 (10.4)
Psoriasis, n (%)	723 (1.7)	258 (3.0)	460 (1.7)	109 (2.0)	1296 (1.8)	612 (4.2)
Cancer, n (%)	940 (2.2)	272 (3.1)	392 (1.4)	68 (1.2)	3030 (4.2)	537 (3.7)

IBD = inflammatory bowel disease, MS = multiple sclerosis, RA = rheumatoid arthritis.

Table 2
Hazard ratios (95% confidence intervals) for the adjusted[a] joint association of immune-mediated inflammatory disease (IMID) and comorbid psychiatric disorders on all-cause mortality.

	IMID	IBD	MS	RA
Matches – no common mental disorder	1.0	1.0	1.0	1.0
IMID – no common mental disorder	**1.75 (1.69, 1.81)**	**1.38 (1.27, 1.50)**	**2.66 (2.44, 2.90)**	**1.72 (1.64, 1.79)**
Matches – common mental disorder	**1.32 (1.28, 1.64)**	**1.34 (1.43, 1.71)**	**1.25 (1.17, 1.34)**	**1.33 (1.29, 1.37)**
IMID – common mental disorder	**2.04 (1.96, 2.11)**	**1.56 (1.27, 1.42)**	**3.31 (2.86, 3.43)**	**1.99 (1.90, 2.09)**
RERI	−0.034 (−0.13, 0.06)	−0.16 (−0.33, 0.021)	0.22 (−0.11, 0.56)	−0.051 (−0.16, 0.062)
AP	−0.017 (−0.062, 0.028)	−0.10 (−0.21, 0.012)	0.071 (−0.031, 0.17)	−0.026 (−0.082, 0.030)
Matches – no depression	1.0	1.0	1.0	1.0
IMID – no depression	**1.70 (1.65, 1.75)**	**1.39 (1.28, 1.49)**	**2.59 (2.39, 2.81)**	**1.65 (1.59, 1.72)**
Matches – depression	**1.56 (1.52, 1.60)**	**1.69 (1.58, 1.79)**	**1.49 (1.38, 1.60)**	**1.54 (1.49, 1.59)**
IMID – depression	**2.38 (2.28, 2.48)**	**1.75 (1.58, 1.93)**	**3.55 (3.22, 3.91)**	**2.35 (2.23, 2.48)**
RERI	**0.12 (0.012, 0.24)**	**−0.33 (−0.53, −0.12)**	**0.47 (0.090, 0.84)**	**0.16 (0.024, 0.30)**
AP	**0.052 (0.0064, 0.098)**	**−0.19 (−0.32, −0.053)**	**0.13 (0.031, 0.23)**	**0.069 (0.013, 0.12)**
Matches – no anxiety disorder	1.0	1.0	1.0	1.0
IMID – no anxiety disorder	**1.75 (1.69, 1.80)**	**1.36 (1.26, 1.47)**	**2.74 (2.54, 2.96)**	**1.70 (1.63, 1.76)**
Matches – anxiety disorder	**1.04 (1.01, 1.07)**	1.04 (0.976, 1.10)	1.000 (0.931, 1.075)	**1.05 (1.02, 1.08)**
IMID – anxiety disorder	**1.58 (1.51, 1.65)**	**1.25 (1.14, 1.38)**	**2.46 (2.21, 2.74)**	**1.55 (1.47, 1.64)**
RERI	**−0.21 (−0.29, −0.12)**	−0.15 (−0.31, 0.013)	−0.28 (−0.60, 0.032)	**−0.19 (−0.30, −0.090)**
AP	**−0.13 (−0.18, −0.075)**	−0.12 (−0.24, 0.0043)	−0.11 (−0.25, 0.021)	**−0.13 (−0.19, −0.057)**
Matches – no bipolar disorder	1.0	1.0	1.0	1.0
IMID – no bipolar disorder	**1.67 (1.63, 1.72)**	**1.29 (1.21, 1.37)**	**2.65 (2.48, 2.83)**	**1.63 (1.58, 1.68)**
Matches – bipolar disorder	**1.49 (1.40, 1.58)**	**1.45 (1.27, 1.65)**	**1.47 (1.25, 1.72)**	**1.52 (1.41, 1.63)**
IMID – bipolar disorder	**2.22 (1.99, 2.47)**	**1.93 (1.57, 2.38)**	**3.12 (2.43, 3.99)**	**2.20 (1.91, 2.53)**
RERI	0.059 (−0.19, 0.31)	0.20 (−0.24, 0.64)	0.0004 (−0.81, 0.81)	0.052 (−0.28, 0.38)
AP	0.027 (−0.085, 0.14)	0.10 (−0.10, 0.31)	0.0001 (−0.27, 0.27)	0.024 (−0.12, 0.17)

[a] Adjusted for sex, socioeconomic status, region of residence, cancer, diabetes, hypertension, chronic lung disease, ischemic heart disease, psoriasis, birth year group; IMID = immune-mediated inflammatory disease; IBD = inflammatory bowel disease; MS = multiple sclerosis; RA = rheumatoid arthritis; RERI = relative excess risk of interaction; AP = attributable proportion; bold indicates statistical significance.

Table 3
Average annual age-specific suicide and suicide attempt rates (95% confidence intervals) per 100,000 population in the immune-mediated inflammatory disease (IMID) cohort and matched cohort.

Age group (years)	Suicide			Suicide attempt		
	IMID	IMID matches	Rate ratio[a] (95% CI)	IMID	IMID matches	Rate ratio[b] (95% CI)
18–44	26.5 (17.0, 36.0)	16.4 (13.0, 19.8)	**1.62 (1.07, 2.45)**	319.9 (286.0, 351.8)	124.1 (114.7, 133.4)	**2.57 (2.26, 2.92)**
45–64	20.0 (12.9, 27.0)	18.2 (15.2, 21.2)	1.10 (0.75, 1.62)	146.3 (127.3, 165.4)	57.6 (52.3, 63.0)	**2.54 (2.16, 2.98)**
≥65	9.23 (3.20, 15.2)	15.6 (12.3, 19.0)	0.59 (0.30, 1.17)	123.0 (101.0, 145.0)	48.1 (42.1, 54.0)	**2.56 (2.06, 3.18)**
Sex						
Male	26.3 (17.0, 35.6)	30.3 (25.9, 34.8)	0.87 (0.59, 1.27)	149.4 (127.3, 171.4)	62.6 (56.2, 68.9)	**2.39 (2.00, 2.86)**
Female	15.7 (10.8, 20.7)	10.6 (8.84, 12.4)	**1.48 (1.03, 2.11)**	214.5 (196.3, 232.7)	80.3 (75.4, 85.3)	**2.67 (2.40, 2.97)**
Overall	19.1 (14.7, 23.6)	16.9 (15.0, 18.8)	1.13 (0.87, 1.47)	193.5 (179.3, 207.8)	74.7 (70.7, 78.6)	**2.59 (2.37, 2.84)**

Cohort * age interaction: a- p = 0.03, b- p = 0.99, Bold = statistically significant; Cohort * sex interaction: a- p = 0.044; b- p = 0.29; Bold = statistically significant.

cohort among those aged 18–44 years. Among females only, suicide rates were also higher in the IMID cohort than in the matched cohort (Table 4). Suicide rates were 3-fold higher among males than females in the matched cohort, but only 1.7-fold higher among males than females in the IMID cohort (p for interaction = 0.044).

The rates of suicide attempts were higher than those of suicide in both cohorts (Table 3), but the relative rates differed. In the IMID cohort, the crude suicide attempt rate was 10-fold higher than the crude suicide rate, whereas in the matched cohort the suicide attempt rate was only 4-fold higher than the suicide rate. Therefore, although the crude suicide rates did not differ between cohorts, the crude suicide attempt rates were higher in the IMID cohort (RR 2.59; 95% CI: 2.37, 2.84). These differences persisted across all age groups (Table 3), and across sexes (Table 3).

After adjusting for sex, birth year group, SES, region of residence, cancer, diabetes, hypertension, chronic lung disease, ischemic heart disease, and psoriasis, the IMID cohort had an 72.5% increased risk of suicide (HR 1.73; 95% CI: 1.33, 2.24). Although the IMID cohort without any CMD did not have a statistically significantly increased risk of suicide, the IMID cohort with any CMD had a 9-fold increased risk of suicide as compared to the matched cohort without any comorbid CMD (Table 4). Findings were similar for depression but not anxiety. Regardless of the presence or absence of comorbid anxiety, the IMID cohort had an increased risk of suicide as compared to the matched cohort without anxiety. Similar findings were observed for bipolar disorder. We did not observe any additive interactions between cohort and comorbid psychiatric disorders for suicide risk.

Table 4
Hazard ratios (95% confidence intervals) for the adjusted[a] joint association of immune-mediated inflammatory disease (IMID) and comorbid psychiatric disorders on suicide.

	IMID	IBD	MS	RA
Matches – no common mental disorder	1.0	1.0	1.0	1.0
IMID – no common mental disorder	1.61 (0.95, 2.73)	0.54 (0.13, 2.24)	1.84 (0.64, 5.31)	**2.37 (1.19, 4.72)**
Matches – common mental disorder	**6.68 (5.21, 8.57)**	**8.64 (5.67, 13.2)**	**5.09 (2.99, 8.67)**	**6.08 (4.18, 8.84)**
IMID – common mental disorder	**9.73 (6.88, 13.8)**	**9.33 (5.02, 17.3)**	**6.23 (2.97, 13.1)**	**11.8 (7.12, 19.5)**
RERI	2.44 (−0.47, 5.36)	1.15 (−3.90, 6.19)	0.30 (−4.10, 4.70)	4.35 (−0.70, 9.39)
AP	0.25 (−0.088, 0.59)	0.12 (−0.77, 1.02)	0.048 (−0.87, 0.97)	0.37 (−0.25, 0.76)
Matches – no depression	1.0	1.0	1.0	1.0
IMID – no depression	1.54 (0.97, 2.45)	0.175 (0.26, 1.99)	1.53 (0.53, 4.39)	**2.29 (1.25, 4.20)**
Matches – depression	**8.96 (7.06, 11.4)**	**9.65 (6.49, 14.3)**	**8.34 (4.96, 14.0)**	**8.57 (5.98, 12.3)**
IMID – depression	**11.9 (8.41, 16.8)**	**9.58 (5.15, 17.8)**	**9.17 (4.42, 19.0)**	**15.2 (9.22, 25.1)**
RERI	2.36 (−1.32, 6.05)	0.22 (−5.41, 5.85)	0.29 (−5.93, 6.52)	5.38 (−1.32, 12.1)
AP	0.20 (−0.15, 0.54)	0.023 (−0.81, 0.86)	0.032 (−0.89, 0.95)	0.35 (−0.034, 0.74)
Matches – no anxiety disorder	1.0	1.0	1.0	1.0
IMID – no anxiety disorder	**1.61 (1.04, 2.48)**	0.95 (0.38, 2.39)	2.14 (0.94, 4.88)	1.82 (0.98, 3.38)
Matches – anxiety disorder	**4.42 (3.49, 5.59)**	**6.28 (4.22, 9.33)**	**3.66 (2.19, 6.09)**	**3.65 (2.56, 5.20)**
IMID – anxiety disorder	**6.82 (4.81, 9.66)**	**6.41 (3.38, 12.2)**	**4.21 (1.89, 9.36)**	**8.38 (5.15, 13.6)**
RERI	1.79 (−0.42, 4.00)	0.19 (−3.74, 4.10)	−0.59 (−4.18, 3.00)	**3.91 (0.22, 7.60)**
AP	0.26 (−0.052, 0.58)	0.029 (−0.77, 0.83)	−0.14 (−1.21, 0.93)	**0.47 (0.15, 0.79)**
Matches – no bipolar disorder	1.0	1.0	1.0	1.0
IMID – no bipolar disorder	**1.70 (1.24, 2.31)**	0.59 (0.27, 1.28)	**2.20 (1.19, 4.09)**	**2.43 (1.60, 3.70)**
Matches – bipolar disorder	**12.0 (9.12, 15.8)**	**9.89 (6.10, 16.0)**	**12.5 (7.114, 22.0)**	**13.3 (8.87, 20.1)**
IMID – bipolar disorder	**15.2 (9.57, 24.0)**	**18.8 (9.75, 36.4)**	**5.46 (1.31, 22.8)**	**20.2 (9.98, 40.9)**
RERI	2.46 (−4.66, 9.57)	9.36 (−2.94, 21.7)	−8.27 (−18.3, 1.76)	5.45 (−8.77, 19.7)
AP	0.16 (−0.27, 0.60)	**0.50 (0.063, 0.93)**	−1.52 (−5.31, 2.28)	0.27 (−0.30, 0.84)

[a] Adjusted for sex, socioeconomic status, region of residence, cancer, diabetes, hypertension, chronic lung disease, ischemic heart disease, psoriasis, birth year group.

3.4. Mortality in individual IMID cohorts

In 2010, the standardized mortality rates varied across the individual IMID cohorts, being highest in the RA cohort (18.0 per 1000; 95% CI 15.0, 21.6), followed by the MS cohort (15.2 per 1000; 95% CI: 11.6, 19.8), and the IBD cohort (11.8 per 1000; 95% CI: 9.56, 14.5). Mortality rates were higher in each of the IMID cohorts as compared to their matched cohorts, however, the magnitude of this effect was higher for the MS (RR 1.79; 95% CI: 1.31, 2.45) and RA cohorts (RR 1.73; 95% CI: 1.41, 2.11) than for the IBD cohort (1.24; 95% CI: 0.98, 1.57).

After adjustment, all of the IMID cohorts had an increased risk of death as compared to their matched cohorts without any CMD, whether or not any CMD was present (Table 2). The presence of any CMD was associated with increased mortality in both the individual IMID and matched cohorts (Table 2). In the IBD cohort, the joint presence of any CMD and IBD had a less than additive risk of mortality whereas we observed the opposite finding in the MS cohort; no interaction was observed in the RA cohort.

Similarly, depression was associated with increased mortality in the individual IMID and their matched cohorts although the additive interactions differed across IMID cohorts. In the IBD cohort we observed a less than additive interaction with depression (AP -19%). However, in the MS and RA cohorts we observed greater than additive interactions in the MS (AP 13%) and RA (AP 6.9%) cohorts such that the joint effects of the IMID and depression increased mortality in these IMID.

In all of the individual IMID cohorts, anxiety was associated with increased mortality. However, we observed a less than additive interaction with anxiety in the RA cohort, and non-significant less than additive interactions in the IBD and MS cohorts. The presence of bipolar disorder was also associated with increased mortality in each individual IMID and their matched cohorts, but no additive interactions were observed for any of the individual IMID cohorts.

3.5. Suicide in individual IMID cohorts

Overall, average annual suicide rates (per 100,000) did not differ between the individual IMID and matched cohorts (Table e2). Findings were similar when stratified by age and sex with two exceptions (Tables e2 and e3). First, males with IBD were less likely to die by suicide than females without IBD. Second, persons aged 18–44 years with RA had a three-fold increased suicide rate versus the matched RA cohort. The rates of suicide attempts were substantially higher than those of suicide in all of the individual IMID and matched cohorts (Table e4). These differences persisted across age groups (Table e4), and sexes (Table e5).

After adjustment, the IBD and MS cohorts without any comorbid CMD did not have an increased risk of suicide as compared to matched cohorts without CMD. This was in contrast to the RA cohort where an increased risk was observed (Table 4). All of the individual IMID cohorts with any comorbid CMD had an increased risk of suicide. Findings were similar for depression and anxiety disorder. We observed an additive interaction between anxiety and RA with an AP of 47%.

4. Discussion

In this population-based study involving three IMID, we evaluated the effects of psychiatric comorbidity on mortality. In the combined, and the individual IMID cohorts, survival was reduced as compared to age-, sex- and geographically-matched cohorts without these IMID, as reported previously [5, 9, 42]. The increased mortality risk in the IMID cohort versus the matched cohort was observed regardless of whether comorbid psychiatric disorders were present. We observed a less than additive interaction between IBD and any CMD on mortality risk, whereas we observed a large positive interaction between MS and any CMD. Similarly, we observed less than additive interactions with depression on mortality risk for IBD, but greater than additive interactions for MS and RA. We observed a less than additive interaction with any anxiety disorder on mortality risk for RA; although the direction of the findings was similar in IBD and MS these did not reach statistical significance.

The generally increased mortality risk associated with all of the psychiatric disorders in the IMID cohorts may reflect several factors. First, depression, anxiety disorders and bipolar disorder are associated with inflammation and immune dysregulation [43, 44]. Depression is also associated with dysregulation of the hypothalamic-pituitary axis

[45], and depression and bipolar disorder are associated with poor health behaviors [46–48]. Persons with psychiatric disorders may experience poorer management of cardiovascular risk factors [49]. To our knowledge, synergistic additive effects of depression on mortality in IMID have not been described previously. However, similar findings have been reported in other chronic disease populations. For example, diabetes and depression have synergistic effects on all-cause mortality and on mortality after myocardial infarction [50, 51]. The mechanisms of these synergistic effects in MS and RA are uncertain but may reflect adverse effects of depression on adherence to IMID-specific therapy, as reported in MS [52], or other disease-specific effects or the adverse effects of depression-associated health behaviors [53–55]. Surprisingly, we saw a less than additive interaction between IBD and depression on mortality. This could reflect biologic differences in the effects of depression on IBD, in the severity of depression in IBD, or in the management of depression in IBD as compared to MS and RA.

Notably, we also observed a less than additive interaction between anxiety and IMID on mortality risk. While studies of the association of anxiety with mortality are relatively few, one large population-based Norwegian study reported that anxiety was associated with reduced all-cause mortality [56]. Another Norwegian study found that anxiety symptoms attenuated the adverse effect of depression on mortality in diabetes [57]. Such findings could reflect increased help-seeking behavior in persons with anxiety [58], or common somatic presentations of anxiety such as palpitations which may lead to increased diagnostic investigations.

After accounting for confounders, the risk of suicide was higher in the IMID cohort than the matched cohort. The relative increase in risk appeared particularly in young individuals and women. A study of chronic respiratory disease similarly found a female-specific increase in suicide risk [13]. Much of the increased suicide risk appeared to be due to the increased burden of psychiatric disorders in the IMID cohorts [7]. Notably, there was a large synergistic effect of anxiety and RA on suicide risk. In the 2010 Global Burden of Disease study, 62.1% of the burden of suicide was attributed to psychiatric disorders [59]; depression accounted for 46.1%, while anxiety disorder accounted for 7.4% and bipolar disorder for 5.4%. Previous findings regarding suicide and IBD have been inconsistent. In a Danish nested case-control study, the rate of suicide was higher in participants with Crohn's disease and ulcerative colitis as compared to age and sex-matched controls [14]. Another study limited to persons with ulcerative colitis diagnosed in Copenhagen reported an increased risk of suicide only among women [42]. However, a British study reported that neither Crohn's disease nor ulcerative colitis was associated with an altered risk of suicide [15]. These studies did not adjust for comorbid psychiatric disorders. Several studies have reported that suicide rates are higher in the MS population than in the general population, although more recent studies have suggested this is no longer true [16, 17]. In a propensity-matched analysis in Manitoba, Canada, MS was associated with a more than two-fold increased risk of suicide [13], which was attenuated after adjusting for comorbid disorders, consistent with our findings. A Finnish study reported that women with hospital-treated RA were more likely to commit suicide than women without RA, and that 80% of women with RA who committed suicide had comorbid hospital-treated depression [60]. In contrast, only 11.1% of men with RA who committed suicide had a history of depression. The association of anxiety disorders with suicide was not reported.

The rate of suicide attempts was higher than the rate of completed suicide in the IMID cohort. While suicide attempts occur with even higher frequency than suicide [61] in the general population too, the relative increase in suicide attempts was higher in the IMID than matched cohorts across all ages and both sexes. Little prior work has assessed suicide attempts in IMID. A British study reported that Crohn's disease was not associated with an altered risk of self-harm, and that ulcerative colitis was associated with a reduced risk of self-harm [15]. In a US study, hospitalized persons with IBD had reduced odds of suicidal ideation or self-harm as compared to hospitalized persons without IBD [62]. Two prior studies have reported conflicting findings regarding the risk of suicide attempts in MS [18, 63]. Our findings are consistent with a Swedish study which reported an increased risk of suicide attempt in the MS population [18]. A British study reported that inflammatory polyarthritis is associated with an increased risk of suicide attempt; RA-specific findings were not reported [15].

Limitations of this study should be recognized. It was conducted in one Canadian province, potentially limiting generalizability. However, the epidemiology of IBD and MS in Manitoba are comparable to other Canadian provinces [64, 65]. Administrative data only capture persons who have sought care for psychiatric disorders from physicians, and those whose symptoms meet a diagnostic threshold. These data are highly specific for identifying suicide attempts but sensitivity is < 50% [26]. Therefore we have likely underestimated the proportion of persons with psychiatric disorders and suicide attempt in our cohorts, but these biases apply to all cohorts and are likely to bias our findings toward the null. Because administrative data lack clinical details, we could not account for the severity of the IMID or the psychiatric disorders or their treatments in our analysis. Nonetheless, this study had several strengths including the population-based design, large sample, use of validated case definitions to identify IMID and psychiatric disorders, and matched control groups.

Depression, anxiety disorders and bipolar disorder are associated with increased mortality risk in persons with IMID. In MS and RA, the effects of depression on mortality risk are greater than the effects of either the IMID or depression alone. In contrast, the effects of anxiety and IMID on mortality are less than the effects of anxiety or IMID alone. The risk of suicide and suicide attempts is elevated in IMID, although psychiatric disorders account for much of this elevated risk. In RA, the joint effects of anxiety and RA accounted for nearly half the risk of suicide. These findings emphasize the importance of identifying and addressing psychiatric disorders and suicidal ideation in persons with IMID.

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Disclosures

Ruth Ann Marrie has no conflicts of interest to declare.

Charles Bernstein has been on the advisory boards of Abbvie Canada, Janssen Canada, Pfizer Canada, Shire Canada, Takeda Canada, Napo Pharmaceuticals and has consulted to Mylan Pharmaceuticals and 4D Pharma. He has received unrestricted educational grants from Abbvie Canada, Janssen Canada, Shire Canada, Pfizer Canada and Takeda Canada. He has been on speaker's bureau of Ferring Canada and Shire Canada.

Jitender Sareen holds stock in Johnson and Johnson.

All other authors have no competing interests to declare.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.genhosppsych.2018.06.001.

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