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Psychiatric comorbidity increases mortality in immune-mediated inflammatory diseases

Ruth Ann Marrie[a,b,*], Randy Walld[c], James M. Bolton[d], Jitender Sareen[d], Scott B. Patten[e], Alexander Singer[f], Lisa M. Lix[b], Carol A. Hitchon[a], Renée El-Gabalawy[g,h], Alan Katz[b,c,f], John D. Fisk[i], Charles N. Bernstein[a], for the CIHR Team in Defining the Burden and Managing the Effects of Psychiatric Comorbidity in Chronic Immunoinflammatory Disease

[a] Department of Internal Medicine, Max Rady College of Medicine, Rady Faculty of Health Sciences, University of Manitoba, Winnipeg, Canada
[b] Department of Community Health Sciences, Max Rady College of Medicine, Rady Faculty of Health Sciences, University of Manitoba, Winnipeg, Canada
[c] Manitoba Centre for Health Policy, Max Rady College of Medicine, Rady Faculty of Health Sciences, University of Manitoba, Winnipeg, Canada
[d] Department of Psychiatry, Max Rady College of Medicine, Rady Faculty of Health Sciences, University of Manitoba, Winnipeg, Canada
[e] Department of Community Health Sciences, Cumming School of Medicine, University of Calgary, Calgary, Canada
[f] Department of Family Medicine, Max Rady College of Medicine, Rady Faculty of Health Sciences, University of Manitoba, Winnipeg, Canada
[g] Department of Clinical Health Psychology, Max Rady College of Medicine, Rady Faculty of Health Sciences, University of Manitoba, Winnipeg, Canada
[h] Department of Anesthesia and Perioperative Medicine, Max Rady College of Medicine, Rady Faculty of Health Sciences, University of Manitoba, Winnipeg, Canada
[i] Departments of Psychiatry, Psychology & Neuroscience, and Medicine, Dalhousie University, Halifax, Canada

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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)

* Corresponding author at: Health Sciences Center, GF-543, 820 Sherbrook Street, Winnipeg, MB R3A 1R9, Canada.
E-mail address: rmarrie@hsc.mb.ca (R.A. Marrie).

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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.