

# Multimorbidity Burden in Rheumatoid Arthritis: A Population-based Cohort Study

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**ABSTRACT. Objective.** To estimate the prevalence and incidence of multimorbidity (MM) in a population-based cohort of patients with rheumatoid arthritis (RA) compared to subjects without RA.

**Methods.** Between 1999–2013, residents of Olmsted County, Minnesota with incident RA who met the 1987 American College of Rheumatology criteria were compared to age- and sex-matched non-RA subjects from the same population. Twenty-five chronic comorbidities from a combination of the Charlson, Elixhauser, and Rheumatic Disease Comorbidity Indices were included, excluding rheumatic comorbidities. The Aalen-Johansen method was used to estimate the cumulative incidence of MM (MM2+;  $\geq 2$  chronic comorbidities) or substantial MM (MM5+;  $\geq 5$ ), adjusting for the competing risk of death.

**Results.** The study included 597 patients with RA and 594 non-RA subjects (70% female, 90% White, mean age 55.5 yrs). At incidence/index date, the prevalence of MM2+ was higher in RA than non-RA subjects (38% RA vs 32% non-RA,  $P = 0.02$ ), whereas prevalence of MM5+ was similar (5% RA vs. 4% non-RA,  $P = 0.68$ ). During follow-up (median 11.6 yrs RA, 11.3 yrs non-RA), more patients with RA developed MM2+ (214 RA vs 188 non-RA; adjusted HR 1.39, 95% CI 1.14–1.69). By 10 years after RA incidence/index, the cumulative incidence of MM2+ was 56.5% among the patients with RA (95% CI 56.5–62.3%) compared with 47.9% among the non-RA (95% CI 42.8–53.7%). Patients with RA showed no evidence of increase in incidence of MM5+ (adjusted HR 1.17, 95% CI 0.93–1.47).

**Conclusion.** Patients with RA have both a higher prevalence of MM at the time of RA incidence as well as increased incidence thereafter.

*Key Indexing Terms:* comorbidity, rheumatoid arthritis

Rheumatoid arthritis (RA) is characterized by systemic inflammation that can negatively affect multiple body systems, in addition to the joints. Patients with RA are known to have increased risks for cardiovascular disease, interstitial lung disease, osteoporotic fractures, and many other chronic conditions.<sup>1,2,3</sup> Comorbidities in patients with RA have historically been studied one at a time, but the importance of understanding the co-occurrence of multiple conditions has been recognized in recent years.<sup>4</sup> The concept of multimorbidity (MM) differs from comorbidity in 2

ways: it is patient-centric, focusing on the patient instead of the index disease of interest, and it is limited to chronic conditions rather than all comorbidities.<sup>5</sup> This concept is useful in patients with RA because it is reflective of patient complexity and the associated challenges in providing care for patients with RA who have multiple chronic conditions (e.g., the influence of other chronic conditions on RA treatment response).<sup>6</sup>

MM is most commonly defined as the coexistence of 2 or more chronic conditions. However, definitions of 3 or more chronic conditions and definitions based on 5 or more classes of medications have also been used in the literature.<sup>7,8</sup> Further, there is no agreement on the list of conditions that should be considered when assessing MM.<sup>9</sup> The most commonly used indices for the general population are the Charlson Comorbidity Index (CCI) and the Elixhauser Comorbidity Index (ECI).<sup>10,11</sup> The Rheumatic Disease Comorbidity Index (RDCI) and Multimorbidity Index (MMI) were developed for use in patients with rheumatic diseases.<sup>4,12</sup>

MM is highly prevalent in the general population.<sup>13</sup> Almost half of the adults in the United States have at least 1 chronic condition, and roughly 1 in 4 have MM, with even higher rates among people aged > 65 years.<sup>14</sup> The increasing prevalence of people living with MM stems from multiple causes including obesity, unhealthy diets, sedentary lifestyles, environmental changes, increasing lifespans, an aging population, improved diagnoses and disease detection, drug-disease interactions,

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and disease-disease interactions.<sup>15</sup> MM is associated with poor quality of life and high healthcare utilization.<sup>16</sup>

Multiple studies have found a high burden of MM in patients with RA, but the extent of this increase compared to people of similar age and sex without RA has not been well characterized.<sup>17,18</sup> We aimed to estimate the prevalence and incidence of MM in a population-based cohort of patients with RA compared to subjects without RA.

## METHODS

The study included previously identified Olmsted County, Minnesota residents with incident RA between January 1, 1999, and December 31, 2013.<sup>19</sup> The complete inpatient and outpatient medical records for each potential case were manually reviewed by an experienced nurse abstractor using the resources of the Rochester Epidemiology Project (REP), and all patients fulfilled the 1987 American College of Rheumatology (ACR) classification criteria for RA.<sup>20</sup> The REP is a unique medical record linkage system that has provided complete access to inpatient and outpatient medical records of all residents of Olmsted County from all local healthcare providers for more than 50 years. Its history and utility for epidemiological investigations have been described in detail elsewhere.<sup>21</sup> The incidence date was defined as the earliest date when the patient fulfilled at least 4 of the 1987 ACR criteria for RA.

For each patient with RA, a subject without RA of similar age, sex, and calendar year was randomly selected from the same population to form the non-RA comparison cohort. Each non-RA subject was assigned an index date corresponding to the incidence date of the patient with RA.

Information on patient characteristics was collected at RA incidence/index date: age, sex, race/ethnicity (White, American Indian/Alaska Native, Asian, Black or African American, Native Hawaiian or other Pacific Islander, > 1 race, or race unknown), smoking status (current, former, or never), BMI, and obesity (BMI  $\geq 30$  kg/m<sup>2</sup>). Data on positivity for rheumatoid factor (RF) and anticyclic citrullinated peptide antibody (ACPA) were also abstracted from the medical records. Patients positive for either RF or ACPA were considered seropositive.

**Definition of comorbidity, MM, and substantial MM.** A list of comorbidities relevant to patients in the general population and those with rheumatic diseases was developed by combining lists from the most commonly used indices: CCI, ECI, and RDCI.<sup>10,12,22</sup> Additional conditions in the MMI were not included because the diagnostic code lists for the MMI were unpublished and could not be obtained from the authors after repeated inquiries.<sup>4</sup> Diagnostic codes from all healthcare providers in Olmsted County for a period beginning 4 years prior to the RA incidence/index date until last follow-up were used to define 25 chronic medical conditions, including cancer, cerebrovascular disease, chronic pulmonary disease, heart failure, dementia, and myocardial infarction from the CCI; diabetes mellitus, metastatic cancer, valvular disease, liver disease, paralysis, peripheral vascular disorders, renal failure, alcohol and substance abuse, coagulopathy, deficiency anemias, depression, hypertension, hypothyroidism, psychoses, other neurological disorders, pulmonary circulation disorders, and HIV/AIDS from the ECI; and spine, hip, or leg fractures from the RDCI. Diagnostic codes assigned to each comorbidity category were as specified in each index's literature. At least 2 diagnostic codes at least 30 days apart were required to define each comorbidity with the second occurrence of the code used as the diagnosis date of the comorbidity. Rheumatic diseases (i.e., RA) and RA extraarticular manifestations (e.g., interstitial lung disease, secondary Sjögren syndrome, vasculitis) were not included as comorbidities. MM was defined as the presence of  $\geq 2$  chronic conditions (MM2+). Due to the high prevalence of hypertension, it was suspected *a priori* that patients meeting the MM2+ definition would primarily have hypertension plus 1 other condition. A second definition of substantial MM, defined as the presence of

$\geq 5$  chronic conditions (MM5+), was examined to capture patients with higher disease complexity and/or disease burden.

**Statistical methods.** Descriptive statistics (mean, SD, count, percentage) were used to summarize patient characteristics as well as the prevalence of comorbidities, MM2+, and MM5+ at index/incidence date. Comparisons between groups at index/incidence date were performed using chi-square test, Fisher exact test, or Mann-Whitney-Wilcoxon rank-sum test.

Cumulative incidence adjusted for the competing risk of death was estimated for each comorbidity, MM2+, and MM5+ using Aalen-Johansen methods.<sup>23</sup> These methods are similar to the Kaplan-Meier method with censoring of patients who were still alive at last follow-up. However, patients who died before experiencing MM2+ or MM5+ were appropriately accounted for to avoid overestimation of the rate of occurrence of MM, which can occur if such patients are simply censored at death. These methods also account for any differences in the mortality rates of the RA and non-RA cohorts. Patients who experienced comorbidity, MM2+, or MM5+ prior to RA incidence or index date were excluded from the cumulative incidence and Cox model calculations. Cox proportional hazard models adjusted for age, sex, calendar year of RA incidence/index date, obesity, and smoking were used to compare the rates of development of each comorbidity and MM between groups. A group by calendar year interaction term was used to assess whether trends over time differed by group. A *P* value of < 0.05 was considered statistically significant for all analyses. Analyses were performed using R 3.6.2 (R Foundation for Statistical Computing). This study was approved by institutional review boards of Mayo Clinic (IRB #17-002593) and Olmsted Medical Center (IRB #017-OMC-17).

## RESULTS

The study included a total of 597 patients with RA and 594 non-RA subjects (Table 1). The RA cohort had a mean (SD) age of 55.5 (15.3) years, was 70% female and 90% White, and 40% were obese at RA incidence. The non-RA cohort had a

Table 1. Characteristics of patients with RA and comparators without RA at incidence/index date.

	RA, n = 597	Non-RA, n = 594
Age, yrs, mean (SD)	55.5 (15.3)	55.4 (15.3)
Sex, female	419 (70)	416 (70)
Race		
Black or African American	16 (3)	17 (3)
White	538 (90)	542 (91)
Other	43 (7)	35 (6)
BMI, kg/m <sup>2</sup> , mean (SD)	29.2 (6.7)	29.3 (6.9)
Obesity, BMI $\geq 30$ kg/m <sup>2</sup>	241 (40)	230 (39)
Smoking status		
Never	313 (52)	349 (59)
Former	191 (32)	155 (26)
Current	93 (16)	90 (15)
No. of nonrheumatic comorbidities at incidence/index		
0	225 (38)	245 (41)
1	144 (24)	161 (27)
2	108 (18)	91 (15)
3	65 (11)	49 (8)
4	26 (4)	23 (4)
5+	29 (5)	25 (4)

Values are expressed as n (%) unless otherwise stated. RA: rheumatoid arthritis.

mean age of 55.4 (15.3) years, was 70% female and 91% White, and 39% were obese at index date. Some differences were noted in smoking status between RA and non-RA groups, primarily among proportions of former smokers (current: 16% vs 15%; former: 32% vs 26%). Within the RA cohort, there were 209 RF/ACPA-negative patients and 388 RF/ACPA-positive patients (Table 2). RF/ACPA-positive patients were more diverse (87% vs 96% White,  $P = 0.002$ ). The median length of follow-up was 11.6 (IQR 7.9–15.5) years for RA and 11.3 (IQR 8.1–15.3) for non-RA subjects. During follow-up, 121 patients with RA and 92 non-RA subjects died.

**Prevalence and incidence of MM.** At RA incidence/index date, significantly more patients with RA had MM2+ (228 [38%] vs 188 [32%],  $P = 0.02$ ), but not MM5+ (29 [5%] vs 25 [4%],  $P = 0.68$ ; Table 3). Patients with RA were also significantly more likely to develop MM2+ (10-yr cumulative incidence [95% CI]: 56.5 [51.3–62.3] vs 47.9 [42.8–53.7]; HR 1.39 [95% CI 1.14–1.69]), but showed no significant difference in MM5+ compared to non-RA subjects (26.8 [23.1–31.1] vs 22.1 [18.7–26.2]; adjusted HR 1.17 [0.93–1.47]; Figure 1).

No significant differences were found in incident rates of MM2+ or MM5+ between RF/ACPA-positive vs -negative patients (Figure 2). The RF/ACPA-negative group showed higher prevalence of MM2+ and MM5+ at RA incidence (91/209 [44%] vs 137/388 [35%],  $P = 0.05$ , and 17/209 [8%] vs 12/388 [3%],  $P = 0.009$ , respectively; Table 4).

**Prevalence and incidence of individual comorbidities.** The most common comorbidity in both groups was hypertension (Table 3). When hypertension was excluded from MM2+ and

Table 2. Characteristics of seronegative and seropositive patients with RA at RA incidence date.

	Seronegative, n = 209	Seropositive, n = 388
Age, yrs, mean (SD)	56.6 (16.0)	54.9 (14.9)
Sex, female	149 (71)	270 (70)
Race		
Black or African American	4 (2)	12 (3)
White	200 (96)	338 (87)
Other	5 (2)	38 (10)
BMI, kg/m <sup>2</sup> , mean (SD)	28.9 (6.5)	29.4 (6.8)
Obesity, BMI $\geq$ 30 kg/m <sup>2</sup>	74 (35)	167 (43)
Smoking status		
Never	120 (57)	193 (50)
Former	65 (31)	126 (32)
Current	24 (12)	69 (18)
No. of nonrheumatic comorbidities at RA incidence		
0	70 (33)	155 (40)
1	48 (23)	96 (25)
2	40 (19)	68 (18)
3	26 (12)	39 (10)
4	8 (4)	18 (5)
5+	17 (8)	12 (3)

Values are expressed as n (%) unless otherwise stated. RA: rheumatoid arthritis

MM5+, the increased risk of MM2+ and MM5+ in RA vs non-RA persisted.

Patients with RA showed significantly increased prevalence of hypothyroidism and chronic pulmonary disease at index/incidence date compared to the non-RA subjects (Table 3). During follow-up, patients with RA showed increased incidence of deficiency anemias, depression, and liver disease compared to non-RA subjects.

**MM burden.** To estimate the overall comorbidity burden, incidence of MM2+ and MM5+ were also estimated including prevalent cases (Figure 1). For patients with RA, when including prevalent cases, the 10-year cumulative incidence of MM2+ was 73.1% (95% CI 69.4–77%; vs 64.4%, 95% CI 60.3–68.7% for non-RA subjects) and of MM5+ was 30.3% (95% CI 26.6–34.6%; vs 25.4%, 95% CI 21.9–29.5%). Within the RA cohort, when including prevalent cases, the 10-year cumulative incidences for MM2+ and MM5+ in RF/ACPA-positive patients were 71.7% (95% CI 67.1–76.6%) and 26.8% (22.4–32.1%) and for RF/ACPA-negative patients were 75.9% (69.8–82.5%) and 36.9% (30.4–44.8%).

## DISCUSSION

Patients with RA had a higher prevalence of MM at RA incidence and a higher incidence of MM2+ during follow-up compared to non-RA subjects. RF/ACPA-negative patients with RA had more morbidities at RA incidence than those who were RF/ACPA-positive, but both subgroups had similar incidence of MM2+ and MM5+ after RA incidence.

Comparability across studies is challenging because there is no standardized list of conditions to include when defining MM, though separately both the Charlson and Elixhauser indices are often cited.<sup>9</sup> Despite this, our findings of a high prevalence of MM in patients with RA are consistent with other reports. A UK-based RA inception cohort reported that the proportion of RA patients with at least 1 comorbidity at RA incidence increased from 29% in 1990 to 51% in 2010.<sup>24</sup> Radner, *et al* reported 62% of patients in Brigham and Women's RA Sequential Study (BRASS) had 1 comorbidity and 36% had at least 2 comorbidities based on a list of 40 morbidities that included the 26 we used and some others with low prevalence (e.g., constipation, hearing loss, psoriasis).<sup>4</sup> Similar prevalence of 65% for 1 comorbidity and 34% for 2 comorbidities were found in the Comorbidities in RA (COMORA) study, which included a list of 17 comorbidities that largely overlapped the list used in this study.<sup>17</sup> Consistent with our findings, all reports listed hypertension as the most common individual comorbidity. Longitudinal examination of the accumulation of morbidities after RA incidence has not been studied extensively. Consistent with our findings, Yoshida, *et al* reported an increased accumulation of morbidities in patients with RA compared to those without RA in the Nurses' Health Study, and Nikiphorou, *et al* reported similar findings in a UK cohort.<sup>18,25</sup> Using MarketScan data from 2006 to 2015, England, *et al* showed a greater burden of MM at RA diagnosis and significantly higher accrual over time in patients with RA vs without RA.<sup>26</sup>



Table 3. Prevalence at RA incidence/index date and cumulative incidence rate of comorbidities, multimorbidity ( $\geq 2$  comorbidities), and substantial multimorbidity ( $\geq 5$  comorbidities) that developed during follow-up in 597 patients with RA compared to 594 subjects without RA.

Comorbidity <sup>a</sup>	No. of Patients Prior to RA Incidence/Index, n (%)	OR (95% CI) Comparing Prior Events	No. of Events After RA Incidence/Index Date, n	Cumulative Incidence at 10 yrs in Patients With RA, % (95% CI)	Cumulative Incidence at 10 yrs in Non-RA Subjects, % (95% CI)	RA vs Non-RA, HR (95% CI) <sup>b</sup>
Alcohol abuse	10 (1.7) / 10 (1.7)	0.99 (0.37–2.69)	17 / 15	3.0 (1.9–4.9)	1.9 (1.0–3.5)	1.05 (0.53–2.11)
Deficiency anemias	54 (9) / 37 (6.2)	1.50 (0.95–2.38)	144 / 119	23.9 (20.3–28.1)	19.2 (16.0–23.2)	1.33 (1.05–1.70)
Cancer	19 (3.2) / 31 (5.2)	0.60 (0.31–1.11)	65 / 64	9.7 (7.5–12.7)	9.9 (7.6–13.0)	1.00 (0.71–1.42)
Heart failure	11 (1.8) / 15 (2.5)	0.72 (0.3–1.71)	46 / 41	8.0 (5.9–10.7)	6.5 (4.6–9.0)	1.11 (0.73–1.69)
Coagulopathy	4 (0.7) / 0 (0)	–	21 / 21	2.9 (1.7–4.7)	3.4 (2.1–5.4)	1.02 (0.56–1.88)
Dementia	2 (0.3) / 3 (0.5)	0.66 (0.06–5.8)	25 / 21	3.3 (2.0–5.5)	2.4 (1.3–4.2)	1.26 (0.70–2.26)
Depression	61 (10.2) / 68 (11.4)	0.88 (0.6–1.29)	115 / 86	20.8 (17.4–24.8)	14.4 (11.6–18.0)	1.35 (1.02–1.79)
Diabetes mellitus	61 (10.2) / 63 (10.6)	0.96 (0.65–1.42)	57 / 56	7.8 (5.7–10.6)	10.1 (7.7–13.3)	0.96 (0.67–1.39)
Drug abuse	7 (1.2) / 5 (0.8)	1.40 (0.38–5.62)	17 / 10	2.3 (1.3–4.1)	1.5 (0.7–3.2)	1.68 (0.77–3.68)
Fracture of spine, hip, or leg	7 (1.2) / 5 (0.8)	1.40 (0.38–5.62)	26 / 15	4.2 (2.8–6.5)	2.0 (1.0–3.7)	1.82 (0.96–3.44)
Hypertension	207 (34.7) / 193 (32.5)	1.10 (0.86–1.41)	141 / 122	32.7 (28.1–38.1)	29.5 (25.0–34.8)	1.28 (1.00–1.63)
Hypothyroidism	96 (16.1) / 63 (10.6)	1.61 (1.13–2.31)	59 / 61	10.8 (8.2–14.1)	11.1 (8.5–14.4)	1.08 (0.75–1.55)
Liver disease	8 (1.3) / 6 (1)	1.33 (0.40–4.68)	33 / 18	5.0 (3.4–7.3)	2.5 (1.5–4.4)	1.89 (1.06–3.36)
Metastatic cancer	3 (0.5) / 10 (1.7)	0.30 (0.05–1.15)	21 / 19	3.2 (2.0–5.1)	3.2 (1.9–5.1)	1.08 (0.58–2.02)
Myocardial infarction	13 (2.2) / 13 (2.2)	0.99 (0.42–2.35)	27 / 38	4.0 (2.6–6.2)	4.8 (3.3–7.1)	0.70 (0.43–1.15)
Other neurological disorders	27 (4.5) / 25 (4.2)	1.08 (0.59–1.96)	111 / 90	15.8 (12.8–19.4)	15.6 (12.6–19.3)	1.23 (0.93–1.63)
Paralysis	3 (0.5) / 3 (0.5)	0.99 (0.13–7.46)	10 / 12	1.7 (0.9–3.3)	1.7 (0.8–3.3)	0.86 (0.37–1.99)
Pulmonary circulation disorders	9 (1.5) / 11 (1.9)	0.81 (0.29–2.17)	38 / 31	5.3 (3.7–7.7)	5.2 (3.5–7.6)	1.22 (0.76–1.97)
Psychoses	61 (10.2) / 42 (7.1)	1.5 (0.97–2.31)	69 / 71	11.4 (8.8–14.7)	12.9 (10.2–16.3)	1.00 (0.71–1.39)
Chronic pulmonary disease	93 (15.6) / 60 (10.1)	1.64 (1.15–2.36)	104 / 91	19.5 (16.1–23.5)	15.6 (12.6–19.3)	1.20 (0.90–1.59)
Peripheral vascular disorders	21 (3.5) / 16 (2.7)	1.32 (0.65–2.73)	117 / 99	16.9 (13.9–20.5)	14.9 (12.0–18.5)	1.29 (0.99–1.69)
Renal failure	8 (1.3) / 4 (0.7)	2.00 (0.53–9.14)	54 / 44	7.8 (5.8–10.6)	4.9 (3.3–7.2)	1.33 (0.89–1.99)
Cerebrovascular disease	20 (3.4) / 18 (3)	1.11 (0.55–2.25)	38 / 49	5.7 (4.0–8.2)	6.9 (5.0–9.7)	0.81 (0.53–1.24)
Valvular disease	25 (4.2) / 29 (4.9)	0.85 (0.47–1.53)	66 / 58	10.8 (8.3–13.9)	8.6 (6.4–11.5)	1.16 (0.82–1.66)
MM2+	228 (38.2) / 188 (31.6)	1.33 (1.04–1.71)	214 / 188	56.5 (51.3–62.3)	47.9 (42.8–53.7)	1.39 (1.14–1.69)
MM5+	29 (4.9) / 25 (4.2)	1.16 (0.65–2.1)	167 / 139	26.8 (23.1–31.1)	22.1 (18.7–26.2)	1.17 (0.93–1.47)

<sup>a</sup> HIV/AIDS only occurred in 1 non-RA subject. <sup>b</sup> Adjusted for age, sex, calendar year of incidence/index date, smoking, and obesity. MM2+: multimorbidity ( $\geq 2$  comorbidities); MM5+: substantial multimorbidity ( $\geq 5$  comorbidities); RA: rheumatoid arthritis.

Regarding individual chronic conditions, our findings are consistent with others who have previously reported an increased prevalence and/or incidence of hypothyroidism, chronic pulmonary disease, depression, and liver disease in patients with RA.<sup>25</sup> The lack of increased occurrence of cardiovascular outcomes in this contemporary cohort of patients with RA is consistent with our previous findings and those of others.<sup>27,28</sup>

Reasons for the increased prevalence and incidence of MM in patients with RA are manifold. Inflammation is known to contribute to the development of cardiovascular disease and other comorbidities.<sup>29</sup> The systemic inflammation that characterizes RA, which is known to begin before RA symptoms manifest, could explain the higher prevalence of MM at RA incidence and could also explain the development of comorbidities after RA incidence. Increased surveillance of patients with RA could also explain some of the increased prevalence of MM in patients with RA, but this might also result from adverse effects of glucocorticoid use or other RA therapies.<sup>30</sup> Further, the presence of comorbidities complicates RA treatment decisions, as evidence is lacking regarding how to treat real-world patients with comorbidities that may have been

excluded from clinical trials of RA therapies or that are listed as contraindications for RA therapies.

The high proportion of seronegative patients in this RA cohort is consistent with previous findings of increasing incidence of seronegative RA.<sup>19</sup> The higher prevalence of comorbidities at RA incidence in RF/ACPA-negative patients suggests these patients are more medically complex. This complexity may contribute to our earlier findings regarding a delay in diagnosis of RA for RF/ACPA-negative patients.<sup>31</sup> Both the high prevalence of comorbidities and the delay in diagnosis of RA may have long-term implications for the treatment and remission of these patients.

These findings underscore the complexity of caring for patients with RA, since a large proportion of these patients have multiple chronic conditions. This complexity makes healthcare decision-making more challenging than in patients without RA. In addition, patients with rheumatic diseases are less likely to receive optimal health maintenance and preventive care services.<sup>32</sup> Therefore, there is an increasing need for rheumatology care models that provide support for addressing MM and for improved coordination of healthcare between rheumatologists and primary care providers.

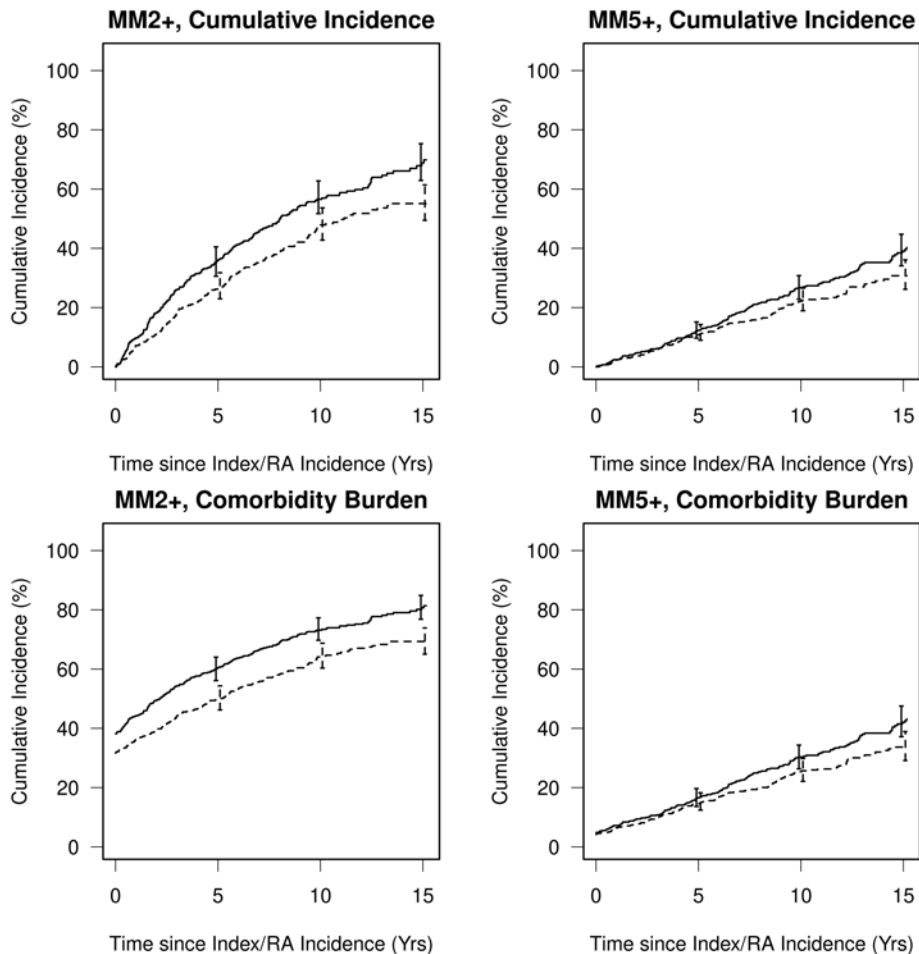


Figure 1. Cumulative incidence (top row) and comorbidity burden (prevalence and cumulative incidence combined; bottom row) of multimorbidity in patients with (solid line) and without (dashed line) rheumatoid arthritis. MM2+ is shown in the left panels and MM5+ in the right panels. MM2+: multimorbidity ( $\geq 2$  comorbidities); MM5+: substantial multimorbidity ( $\geq 5$  comorbidities).

Strengths of this study include the well-characterized, population-based cohort of patients who met classification criteria for RA. The comprehensive resources of the REP facilitated identification of all clinically recognized cases of RA in the population and minimized selection bias. The REP resources also facilitated unbiased selection of non-RA comparators from the same population. Further, the duration of follow-up was long (median 11 yrs), which allowed assessment of comorbidity accumulation over time. Study limitations include the use of diagnostic codes to define MM and the retrospective study design, which necessitated that the only diagnoses used were those that came to medical attention and were documented in the medical records. The availability of comprehensive medical records from all providers in the community and the focus on chronic comorbidities minimizes the risk of missing comorbidities of interest, but the accuracy of coded diagnoses can be suboptimal. Standard procedures used in administrative claims studies, such as requiring 2 codes at least 30 days apart, were used to improve reliability of the coded diagnoses. Another limitation was the use of a count of

chronic conditions to define MM burden. While counts are commonly used in studies of MM, equally weighting conditions does not accurately reflect the differing severity of the conditions. Weighted comorbidity indices have been used to predict various outcomes, but weights also have limitations. For example, weights developed using general population data may not apply to patients with RA, and weighting might partially account for intercondition severity but not intracondition severity. Finally, the limited diversity in the Olmsted County population (90% White) may limit the generalizability of these findings to more diverse populations.

In conclusion, patients with RA already have more comorbid conditions than their non-RA counterparts at RA incidence, and they accumulate more comorbid conditions than non-RA subjects throughout the RA disease course. These findings underscore the challenges faced by the providers who care for these complex patients. More research is needed, both to interpret possible disease clusters or trajectories within the accumulation of these comorbidities and to define strategies to reduce the comorbidity burden for patients with RA.

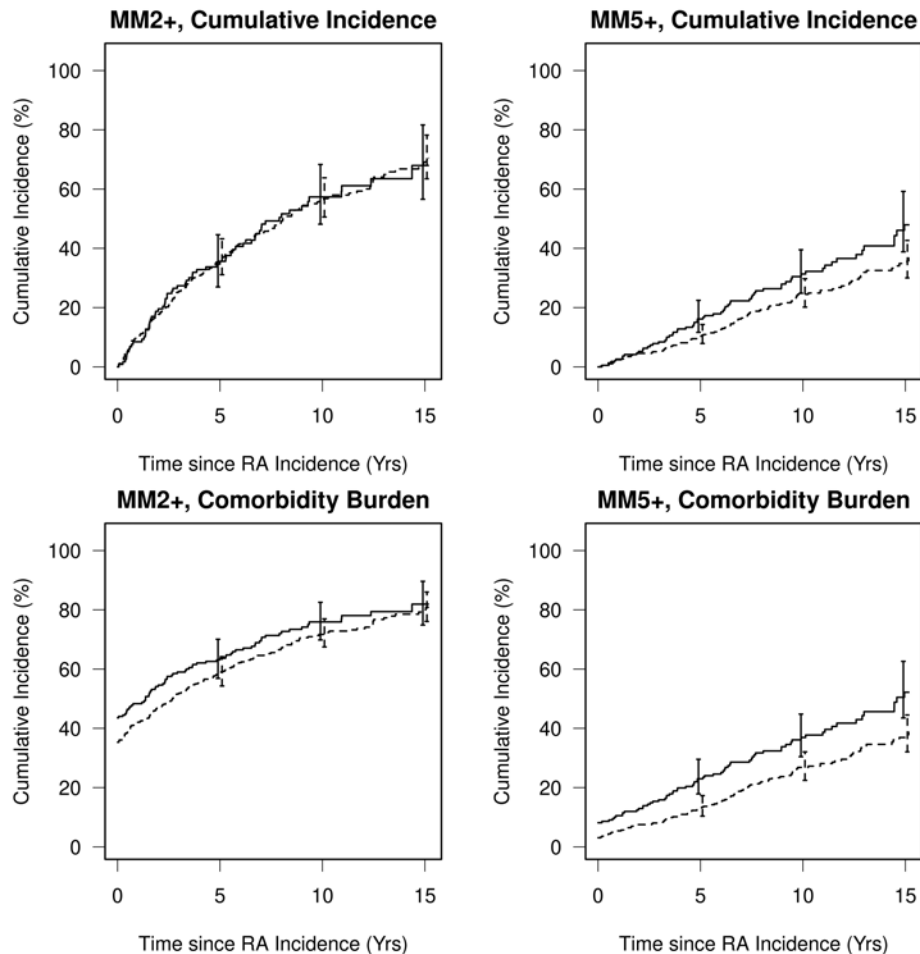


Figure 2. Cumulative incidence (top row) and comorbidity burden (prevalence and cumulative incidence combined; bottom row) of multimorbidity in rheumatoid arthritis patients without (solid line) and with (dashed line) rheumatoid factor and/or anticyclic citrullinated peptide antibody-positivity. MM2+ is shown in the left panels and MM5+ in the right panels. MM2+: multimorbidity ( $\geq 2$  comorbidities); MM5+: substantial multimorbidity ( $\geq 5$  comorbidities).

Table 4. Prevalence at RA incidence/ index date and cumulative incidence rate of multimorbidity ( $\geq 2$  comorbidities), and substantial multimorbidity ( $\geq 5$  comorbidities) that developed during follow-up in 209 RF/ACPA-negative patients and 388 RF/ACPA-positive<sup>a</sup> patients.

Outcome	N (%) of Patients Prior to RA Incidence in RF/ACPA, +/-	OR (95% CI) Comparing Prior Events	No. of Events After RA Incidence Date in RF/ACPA, +/-	Cumulative Incidence at 10 yrs in RF/ ACPA+ Patients, % (95% CI)	Cumulative Incidence at 10 yrs in RF/ ACPA- Patients, % (95% CI)	RF/ACPA+ vs RF/ACPA- <sup>b</sup> , HR (95% CI)
MM2+	137 (35.3) / 91 (43.5)	0.71 (0.49–1.01)	150 / 64	56.2 (50.0–63.2)	57.4 (48.1–68.3)	1.00 (0.74–1.36)
MM5+	12 (3.1) / 17 (8.1)	0.36 (0.15–0.82)	103 / 64	24.5 (20.2–29.7)	31.3 (24.8–39.5)	0.83 (0.60–1.15)

<sup>a</sup>RF/ACPA-positive was defined as positive for either RF or ACPA. <sup>b</sup> Adjusted for age, sex, calendar year of incidence/index date, smoking, and obesity. MM2+: multimorbidity ( $\geq 2$  comorbidities); MM5+: substantial multimorbidity ( $\geq 5$  comorbidities); RA: rheumatoid arthritis; RF: rheumatoid factor/anticyclic citrullinated peptide antibody [positive (+) or negative (-)].

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