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Risk Factors for Dementia in Patients With Incident Rheumatoid Arthritis: A Population-Based Cohort Study

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ABSTRACT. ***Objective.*** Growing evidence suggests that patients with rheumatoid arthritis (RA) have increased risk for dementia. We assessed risk factors for incident dementia in an inception cohort of patients with RA.

Methods. This retrospective population-based cohort study included residents of 8 counties in Minnesota who were ≥ 50 years of age when they met 1987 American College of Rheumatology criteria for incident RA between 1980 and 2014 and were followed until death/migration or December 31, 2019. Patients with dementia before RA incidence were excluded. Incident dementia was defined as 2 relevant International Classification of Diseases, 9th or 10th revision codes at least 30 days apart. Data on sociodemographics, disease characteristics, cardiovascular/cerebrovascular disease (CVD) risk factors, and comorbidities were abstracted from medical records.

Results. The study included 886 patients with RA (mean age 65.1 yrs, 65.2% female). During the follow-up period (median 8.5 yrs), 103 patients developed dementia. After adjusting for age, sex, and calendar year of RA incidence, older age at RA incidence (HR 1.14 per 1 year increase, 95% CI 1.12-1.17), rheumatoid nodules (HR 1.76, 95% CI 1.05-2.95), hypertension (HR 1.84, 95% CI 1.19-2.85), presence of large joint swelling (HR 2.03, 95% CI 1.14-3.60), any CVD (HR 2.25, 95% CI 1.38-3.66), particularly ischemic stroke (HR 3.16, 95% CI 1.84-5.43) and heart failure (HR 1.82, 95% CI 1.10-3.00), anxiety (HR 1.86, 95% CI 1.16-2.97), and depression (HR 2.63, 95% CI 1.76-3.93) were associated with increased risk of dementia. After adjusting for CVD risk factors and any CVD, all covariates listed above were still significantly associated with risk of dementia.

Conclusion. Apart from age, hypertension, depression, and anxiety, all of which are universally recognized risk factors for dementia, clinically active RA and presence of CVD were associated with an elevated risk of dementia incidence among patients with RA.

Key Indexing Terms: cardiovascular disease, dementia, depression, disease activity, rheumatoid arthritis

Alzheimer disease (AD) and related dementias are a group of debilitating disorders that primarily affect the elderly and cause significant limitations in physical, mental, and social capabilities, as well as increased mortality.[1] AD is the most common form of dementia, accounting for up to 80% of dementia cases and affecting approximately 11% of individuals aged ≥ 65 years.[2] AD and related dementias have a decades-long preclinical course preceding development of clinically apparent cognitive impairment and dementia.[3] Prevention of the onset and progression of dementia is a rapidly growing area of research. Less education in early life; traumatic brain injury, hearing loss, hypertension (HTN), alcohol, and obesity in midlife; and hyperlipidemia, diabetes mellitus (DM), smoking, depression, social isolation, and air pollution in later life are potentially modifiable

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risk factors accounting for up to 40% of the risk of dementia.[4] Reduced sleep during middle age was also previously associated with increased risk of dementia.[5] Addressing these modifiable risk factors for dementia offers significant potential for prevention of this incurable disease.

The potential role of inflammation in pathogenesis and risk modification in dementia is an area of growing interest.[6] Chronic systemic inflammation is a hallmark of rheumatoid arthritis (RA). Growing evidence from observational studies shows that RA is associated with an approximately 40% increase in risk of cognitive decline and incident dementia.[7,8] However, the incidence of dementia in RA appears to be on a decline in recent decades, aligning with the practice of earlier initiation of disease-modifying antirheumatic drug (DMARD) treatments and the introduction of biologics.[9] It remains to be established whether this recent decline in the incidence of dementia in RA is a result of better control of the inflammation in RA or a reduction of other risk factors (eg, comorbidities and/or environmental factors), or if it is a consequence of more precise diagnosis of both dementia and RA.

Longitudinal population-based studies assessing risk factors for dementia in RA are scarce.[7] In the present study we aimed to identify risk factors associated with incident dementia in an inception cohort of patients with RA. We hypothesized that RA disease characteristics, among other risk factors, increase the risk of incident dementia.

METHODS

Study design and population. This retrospective, population-based cohort study included an inception cohort of patients with RA ascertained among residents of 8 counties (Olmsted, Dodge, Mower, Goodhue, Wabasha, Freeborn, Steele, and Waseca) in the state of Minnesota using the Rochester Epidemiology Project (REP). The REP is a medical records linkage system that provides essentially complete ascertainment of all residents of Olmsted County, Minnesota, USA, and surrounding counties. It provides comprehensive access to patients' complete medical records from all community medical providers.[10,11] Individuals who were aged ≥ 50 years when they fulfilled at least 4 of the 1987 American College of Rheumatology classification criteria for RA between 1980 and 2014 were included.[12]

Outcome definitions. Incident dementia was defined as 2 International Classification of Diseases, 9th or 10th (ICD-9 or ICD-10, respectively) revision codes for dementia, including "dementia" (290.x, 294.1, F03.x), AD (F00.x, G30.x), "vascular dementia" (F01.x), "dementia in other diseases" (F02.x), or "senile degeneration brain" (331.2, G31.1), at least 30 days apart.[13,14] All cases of "Alzheimer disease and related dementias" were collectively called "dementia." Individuals with incidence of dementia before RA incidence were excluded. All patients were followed through medical record review from inclusion until death/migration or December 31, 2019.

Measures and exposures. Trained nurse abstractors who were blinded to the study hypothesis reviewed complete outpatient and inpatient records of all patients and abstracted information on sociodemographic characteristics and RA disease characteristics (ie, smoking status, radiographic erosions, large joint swelling, joint surgeries, extraarticular features, seropositivity, and erythrocyte sedimentation rate [ESR]). We defined seropositivity as positivity for either rheumatoid factor (RF) and/or anticyclic citrullinated peptide antibodies (anti-CCP) at any time.

Severe extraarticular manifestations were defined according to Malmö criteria and included pericarditis, pleuritis, Felty syndrome, glomerulonephritis, vasculitis, peripheral neuropathy, scleritis, and episcleritis.[15]

We also collected information on the use of conventional synthetic DMARDs (csDMARDs; eg, methotrexate [MTX], hydroxychloroquine, and other csDMARDs), and biologic DMARDs (bDMARDs; ie, tumor necrosis factor-α inhibitors [TNFi] and non-TNFi biologics) during the follow-up. For this study, we defined other csDMARDs as leflunomide, sulfasalazine, azathioprine, gold, d-penicillamine, cyclosporine, and cyclophosphamide.

Data on cardiovascular/cerebrovascular disease (CVD) risk factors (ie, HTN, DM, hyperlipidemia) and CVD events were also abstracted from the medical records at baseline and throughout the follow-up as previously described.[16] The presence of HTN and DM was defined based on physician diagnosis and/or use of antihypertensives, lipid-lowering medications, or antidiabetic medications. Any CVD was defined as coronary heart disease (angina pectoris, coronary artery disease [CAD], myocardial infarction [MI], any coronary revascularization procedure), ischemic stroke, cardiovascular death, intermittent claudication, heart failure (HF), or a combination of any of these.

Depression and anxiety were ascertained based on ICD-9/ICD-10 codes using a definition requiring at least 2 codes ≥ 30 days apart.

Statistical analysis. Descriptive statistics were used to summarize the data. The cumulative incidence of dementia adjusted for the competing risk of death was estimated. Association of each individual risk factor with incident dementia was examined using Cox proportional hazard models. Since most of the RA characteristics (eg, erosions, extraarticular manifestations, medication use) were uncommon at the RA incidence date, we extended the period for assessment of "baseline" variables for 1 year. For consistency, we used the same time period to define all risk factors, since comorbidities diagnosed shortly after RA incidence were likely present before RA incidence. Thus, the "baseline" risk factors included those present at RA incidence or that developed during the first year after RA incidence. Since there were very few dementia events (n = 3) in the first year after RA incidence, the immortal time bias because of this definition would be minimal. Risk factors that developed prior to RA incidence, at RA incidence, or any time after RA incidence and during follow-up were referred to as "ever" and were included in the analysis using time-dependent covariates.

For each risk factor of interest, 2 models were utilized: model 1, adjusting for age, sex, and calendar year of RA incidence; model 2, adding smoking, obesity, HTN, DM, and hyperlipidemia to model 1 with any CVD also included as an adjustor for risk factors of interest that were not CVD-related. Hazard ratios (HRs) with 95% CIs were estimated and reported. Nonlinear effects for continuous variables were assessed using smoothing splines. The proportional hazards assumption was assessed using the Schoenfeld residuals and no violations were found. P values < 0.05 were considered to be statistically significant. Analyses were performed using SAS version 9.4 (SAS Institute) and R 4.0.3 (R Foundation for Statistical Computing). This study was approved by the institutional review boards of the Mayo Clinic (IRB #17-002593) and Olmsted Medical Center (IRB #017-OMC-17). The need for informed consent was waived. Patients who declined the use of their medical records for research purposes were not included in the study, per Minnesota law. This study followed the STROBE (STrengthening the Reporting of OBservational studies in Epidemiology) guidelines for observational studies.[17]

RESULTS

Patients' characteristics. Twelve patients with dementia prior to RA incidence were excluded. A total of 886 patients with incident RA and no dementia prior to RA incidence date were included. Demographics and patient characteristics are shown in Table 1. Mean age was 65.1 years, the majority were women (65.2%) and non-Hispanic White (95.4%), and 62.5% were RF and/or anti-CCP seropositive.

Incidence of dementia. During the median follow-up of 8.5 years,

Table 1. Baseline characteristics of 886 patients with incident RA.

	Value
Sociodemographics	
Age, yrs, mean (SD)	65.1 (10.0)
Sex, female	578.0 (65.2)
Race	
Non-Hispanic White	829 (95.4)
American Indian or Alaska Native	3 (0.3)
Asian	17 (2.0)
Black or African American	8 (0.9)
Native Hawaiian or other Pacific Islander	2 (0.2)
Hispanic	17 (1.9)
Other	4 (0.5)
Unknown	6 (0.7)
Education	
< High school	94 (10.6)
High school	301 (34.0)
Technical school/college	382 (43.1)
Graduate school	45 (5.1)
No documentation	64 (7.2)
CVD risk factors and events	
Smoking status	
Never	364 (41.1)
Current	179 (20.2)
Former	343 (38.7)
Baseline BMI, kg/m^2, mean (SD)	28.7 (6.4)
Obesity (BMI ≥ 30)	311 (35.1)
Hypertension	555 (62.6)
Diabetes mellitus	117 (13.2)
Hyperlipidemia	440 (49.7)
Any CVD[a]	149 (16.8)
Myocardial infarction	24 (2.7)
Heart failure	33 (3.7)
Ischemic stroke	19 (2.1)
Other comorbidities	
Anxiety	97 (10.9)
Depression	189 (21.3)
RA disease characteristics	
RF and/or anti-CCP positive	549 (62.5)
ESR at RA incidence, mm/h, median, (IQR)	22 (11-38)
Highest ESR in the first year after RA incidence, mm/h, median (IQR)	30 (16-49)
Erosive RA	260 (29.3)
Severe extraarticular manifestations	37 (4.2)
Rheumatoid nodules	104 (11.7)
Large joint swelling	544 (61.4)
Arthroscopy	71 (8.0)
Synovectomy	30 (3.4)
Medication use	
Methotrexate	421 (47.5)
Hydroxychloroquine	355 (40.1)
Other DMARDs	140 (15.8)
Biologic	56 (6.3)
Glucocorticoids	580 (65.5)
NSAIDs (traditional)	616 (69.5)
COX-2 inhibitors	171 (19.3)
Salicylate[b]	222 (25.1)
Antihypertensives	447 (50.5)
Lipid-lowering medications	287 (32.4)

Values are n (%) unless otherwise indicated and are shown for baseline (defined as RA incidence date through 1 year after RA incidence). [a] Any CVD: angina pectoris, coronary artery disease, myocardial infarction, any coronary revascularization procedures, ischemic stroke, cardiovascular death, intermittent claudication and/or heart failure. [b] Salicylate: 500 mg/d to 3 g/d for RA. Anti-CCP: anticyclic citrullinated peptide antibodies; COX-2: cyclo-oxygenase-2; CVD: cardiovascular/cerebrovascular disease; DMARD: disease-modifying antirheumatic drug; ESR: erythrocyte sedimentation rate; NSAID: nonsteroidal antiinflammatory drug; RA: rheumatoid arthritis, RF: rheumatoid factor.

103 patients developed dementia. Mean (SD) age at the diagnosis of dementia was 82.3 (7.2) years. Following RA incidence, the cumulative incidence of dementia increased by 2% to 3% every 5 years (Figure).

Risk factors for dementia. After adjusting for age, sex, and year of RA incidence (model 1), we identified several risk factors for dementia, as shown in Table 2. Older age at RA incidence was consistently associated with an increased risk of dementia (HR 1.14 per 1 year increase, 95% CI 1.12-1.17). Presence of rheumatoid nodules (HR 1.76, 95% CI 1.05-2.95), large joint swelling (HR 2.11, 95% CI 1.33-3.34), HTN (HR 1.84, 95% CI 1.19-2.85), HF (HR 2.72, 95% CI 1.29-5.74), depression (HR 2.23, 95% CI 1.36-3.67), and antihypertensive medication use (HR 1.72, 95% CI 1.13-2.64) at baseline was significantly associated with development of incident dementia during the follow-up. Large joint swelling (HR 2.03, 95% CI 1.14-3.60), any CVD (HR 2.25, 95% CI 1.38-3.66), anxiety (HR 1.86, 95% CI 1.16-2.97), and depression (HR 2.63, 95% CI 1.76-3.93) at any time after RA incidence increased the risk of dementia. Among CVD conditions, ischemic stroke (HR 3.16, 95% CI 1.84-5.43) and HF (HR 1.82, 95% CI 1.10-3.00) significantly increased risk of dementia, whereas associations with MI did not reach statistical significance (HR 1.51, 95% CI 0.80-2.88, $P = 0.10$). The presence of DM at baseline or ever was associated with an approximately 50% increase in the risk of dementia, although the associations did not reach statistical significance.

After adjusting for CVD risk factors and CVD (model 2), all the risk factors listed above were still significantly associated with dementia (Table 2).

Sex, race, education, smoking, obesity, hyperlipidemia, RF/anti-CCP positivity, erosive RA, severe extraarticular manifestations of RA, joint surgeries (arthroplasty, synovectomy), ESR (at RA incidence and highest value in the first year after RA incidence), and ever use of csDMARDs, bDMARDs, or nonsteroidal antiinflammatory drugs were not associated with the risk of dementia among patients with RA (Table 2).

DISCUSSION

In this population-based cohort study of an inception cohort of patients with RA with a long follow-up, we comprehensively assessed risk factors for the incidence of dementia. Apart from age, HTN, depression, and anxiety, all of which are universally recognized risk factors for dementia, RA disease characteristics (ie, large joint swelling and rheumatoid nodules) and presence of any CVD were associated with incident dementia.

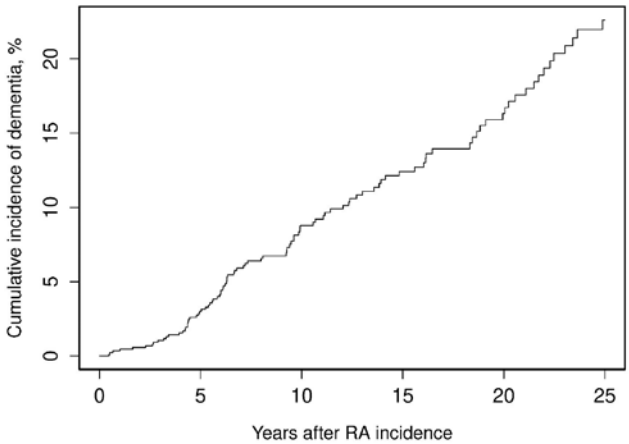

Figure. Cumulative incidence of dementia after RA incidence. RA: rheumatoid arthritis.

The first noteworthy finding from this study is that 2 RA disease characteristics (large joint swelling and rheumatoid nodules) are associated with increased risk of incident dementia, which supports our main hypothesis. Although these measures have not been previously examined in relation to dementia in longitudinal population-based RA cohorts, this finding aligns with the existing literature from previous studies in RA and the general population. Indeed, soluble mediators of inflammation (eg, TNF-α, interleukin [IL]-1β, IL-6) that mediate RA pathogenesis have been associated with mild cognitive impairment (MCI) as well as dementia in the general population.[18-20] Previous studies in patients with RA have shown that the risk of MCI is higher in patients with higher disease activity scores.[21,22] This association can be potentially explained through the effects of systemic inflammation and neuroinflammation. The soluble mediators of inflammation in RA increase the permeability of the blood–brain barrier and stimulate the microglia in the central nervous system. The presence of activated microglia is associated with neuroinflammation and neuronal damage.[23-25] Somewhat surprisingly, inflammatory markers (ESR at RA incidence, highest ESR in the first year after RA incidence) were not associated with increased risk of dementia in this study. A potential explanation may be the high variability in ESR across the disease course. Thus, single-timepoint inflammatory markers may not be reliable indicators of cumulative inflammatory burden and its association with dementia.[26] Indeed, association between inflammatory markers assessed at single timepoints and dementia have been inconsistent, with some studies showing an increased risk and others not finding associations.[27] Studies are ongoing by our group to further evaluate the association between serial measures of inflammatory markers and risk of dementia.

Although erosions are a proxy for RA severity, they were not associated with dementia in our study. One reason could be that analyses were adjusted for disease duration, which is one of the main drivers of erosive burden in RA. Anti-CCP and/or RF positivity were not associated with risk of dementia in our study, even though the association between autoimmunity and dementia appears biologically plausible, particularly with regard to anti-CCP. Indeed, both RA and dementia are conditions with increased citrullination.[28] Previous studies have shown an association of anti-CCP with AD in the general population.[29] Anti-CCP positivity indicates higher citrullination and more extensive peptidylarginine deaminase-mediated damage to myelin sheath proteins in AD.[30] However, the association between anti-CCP and dementia in RA has not been previously explored. Variable association of APO-ε4 allele with seropositivity could be a possible reason for lack of correlation between RF/anti-CCP positivity and dementia.[31] No information on APO-ε4 status was available in this study. The prognostic utility of RF and anti-CCP for the risk of dementia in RA overall and by

Table 2. Risk factors for incident dementia in patients with RA.

	Model 1[a] HR (95% CI)	Model 2[b] HR (95% CI)
Sociodemographics		
Age, yrs	**1.14 (1.12-1.17)**	**1.13 (1.10-1.17)**
Sex, male	0.98 (0.64-1.48)	0.74 (0.45-1.19)
Index calendar year	0.98 (0.96-1.01)	0.98 (0.95-1.02)
Race, non-White	1.42 (0.44-4.54)	1.71 (0.51-5.68)
Education, ≤ high school	0.73 (0.49-1.11)	0.69 (0.44-1.08)
CVD risk factors		
Smoking status at index date		
Never	Ref	Ref
Current	1.12 (0.61-2.08)	1.43 (0.74-2.75)
Former	1.19 (0.77-1.83)	1.48 (0.92-2.39)
Baseline BMI > 30 kg/m^2	1.27 (0.81-2.00)	1.06 (0.63-1.78)
Hypertension		
Baseline	**1.84 (1.19-2.85)**	**2.79 (1.44-5.40)**
Ever	1.12 (0.66-1.91)	0.87 (0.48-1.56)
Diabetes mellitus		
Baseline	1.49 (0.88-2.54)	1.10 (0.40-3.06)
Ever	1.46 (0.91-2.34)	1.48 (0.87-2.52)
Hyperlipidemia		
Baseline	1.38 (0.88-2.17)	1.27 (0.69-2.36)
Ever	1.27 (0.81-2.00)	0.87 (0.51-1.47)
Antihypertensive medication use		
Baseline	**1.72 (1.13-2.64)**	1.63 (0.92-2.89)
Ever	1.36 (0.84-2.21)	1.25 (0.49-3.17)
Lipid-lowering medication use		
Baseline	1.07 (0.64-1.81)	0.73 (0.37-1.44)
Ever	1.10 (0.71-1.70)	0.62 (0.33-1.15)
CVD conditions		
CVD, overall		
Baseline	1.37 (0.86-2.19)	1.35 (0.84-2.20)
Ever	**2.25 (1.38-3.66)**	**2.45 (1.47-4.07)**
Myocardial infarction		
Baseline	1.12 (0.35-3.56)	0.91 (0.28-2.95)
Ever	1.51 (0.80-2.88)	1.45 (0.75-2.80)
Heart failure		
Baseline	**2.72 (1.29-5.74)**	1.49 (0.46-4.83)
Ever	**1.82 (1.10-3.00)**	**3.28 (1.90-5.67)**
Ischemic stroke		
Baseline	1.46 (0.45-4.72)	**2.89 (1.33-6.27)**
Ever	**3.16 (1.84-5.43)**	**1.84 (1.12-3.04)**
Other comorbidities		
Anxiety		
Baseline	1.50 (0.77-2.93)	1.06 (0.47-2.38)
Ever	**1.86 (1.16-2.97)**	**1.75 (1.04-2.95)**
Depression		
Baseline	**2.23 (1.36-3.67)**	**2.33 (1.33-4.10)**
Ever	**2.63 (1.76-3.93)**	**2.76 (1.78-4.28)**
RA disease characteristics		
RF/anti-CCP positive (baseline)	1.22 (0.81-1.82)	1.18 (0.77-1.82)
Highest ESR in first year, mm/h	1.00 (0.99-1.01)	1.00 (0.99-1.01)
ESR at RA incidence, mm/h	1.00 (0.99-1.01)	1.00 (0.99-1.01)
Erosive RA		
Baseline	1.12 (0.72-1.74)	1.15 (0.71-1.85)
Ever during follow-up	1.18 (0.79-1.75)	1.36 (0.88-2.10)
Rheumatoid nodules		
Baseline	**1.76 (1.05-2.95)**	**2.02 (1.17-3.50)**
Ever during follow-up	1.32 (0.84-2.06)	1.58 (0.98-2.54)

Table 2. Continued.

	Model 1[a] HR (95% CI)	Model 2[b] HR (95% CI)
Severe extraarticular manifestations		
Baseline	1.20 (0.44-3.31)	1.18 (0.41-3.37)
Ever	1.29 (0.68-2.44)	1.25 (0.64-2.44)
Large joint swelling		
Baseline	**2.11 (1.33-3.34)**	**2.26 (1.35-3.79)**
Ever	**2.03 (1.14-3.60)**	**2.41 (1.22-4.73)**
Synovectomy[c]	1.00 (0.49-2.05)	0.96 (0.46-2.02)
Arthroscopy[c]	0.73 (0.46-1.16)	0.79 (0.48-1.29)
No. of csDMARDs used[c]	0.94 (0.77-1.14)	0.95 (0.77-1.15)
No. of bDMARD used[c]	0.77 (0.48-1.24)	0.92 (0.59-1.42)
RA medications, ever used		
Methotrexate	1.13 (0.72-1.75)	1.17 (0.72-1.88)
Hydroxychloroquine	0.71 (0.47-1.07)	0.72 (0.46-1.13)
Other DMARDs	1.16 (0.71-1.90)	1.19 (0.68-2.07)
bDMARD use	0.82 (0.37-1.82)	1.18 (0.52-2.67)
Glucocorticoids	1.46 (0.86-2.46)	1.48 (0.86-2.56)
NSAIDs	1.11 (0.59-2.07)	1.07 (0.50-2.28)
COX-2 inhibitors	0.88 (0.57-1.36)	0.80 (0.48-1.32)
Salicylate[d]	0.79 (0.49-1.28)	0.81(0.50-1.33)

Values in bold are statistically significant. The covariates were analyzed as time-dependent to represent factors that developed during follow-up. [a] Model 1 adjusts for age, sex, and calendar year of RA incidence. [b] Model 2 adjusts for factors in Model 1 plus smoking, obesity, hypertension, diabetes mellitus, and hyperlipidemia, with any CVD also included as an adjustor for risk factors of interest that were not CVD-related. [c] Ever during follow-up. [d] Salicylate: 500 mg/d to 3 g/d for RA. Anti-CCP: anticyclic citrullinated peptide antibodies; bDMARD: biologic disease-modifying antirheumatic drug; COX-2: cyclooxygenase-2; csDMARD: conventional synthetic disease-modifying antirheumatic drug; CVD: cardio/cerebrovascular disease; DMARD: disease-modifying antirheumatic drug; ESR: erythrocyte sedimentation rate, NSAID: nonsteroidal antiinflammatory drug; RA: rheumatoid arthritis, RF: rheumatoid factor.

APO-ε4 carrier status requires further elucidation. Alternatively, the lack of association between erosions and RF/anti-CCP with dementia could indicate indirect effects of RA (eg, mediation through CAD).

The second key finding in this study is that CVD risk factors and CVD events significantly increased the risk of dementia in patients with RA. Epidemiological studies have consistently shown that advanced age, midlife HTN, DM, obesity, smoking, and hyperlipidemia are associated with increased risk for dementia in the general population.[32,33] These risk factors have also been shown to accelerate the progression of MCI to AD.[34] Further, CVD events (stroke, HF, atrial fibrillation, and CAD) have been associated with dementia.[35] In patients with RA, chronic systemic inflammation may interact with comorbidities, such as CVD leading to accelerated cognitive decline. Ungprasert et al found an approximately 40% increased risk of dementia in patients with RA compared to the general population that can be attributed to this adverse CVD profile superimposed on systemic inflammation.[8] Indeed, among elderly patients with RA, the risk of dementia increases with increasing CVD risk (presence of CVD risk factors and any CVD events).[36] We extended these findings by evaluating associations with individual CVD risk factors and CVD events.

In the current study, HTN at baseline was strongly associated with incident dementia. This is concordant with findings in the general population[32] but has not been previously shown in patients with RA. The association of antihypertensive use at baseline with dementia in our study can be a result of confounding by indication (ie, HTN). Although DM has been associated with dementia risk in the general population,[37] its association with increased dementia risk in our study did not reach statistical significance. This is likely a result of insufficient statistical power in our study. Hyperlipidemia and obesity were also not associated with an increased risk of dementia in our study. Similar to fluctuations in the levels of inflammation, there is substantial variability in BMI and lipid measures in RA across the lifespan and RA disease course.[26,38] In the general population, hyperlipidemia in midlife has been associated with an increased risk of dementia, whereas in late life, the relationship is reversed.[39] Weight loss in late life typically precedes the onset of dementia in the general population.[40] Examining temporal associations between CVD risk factors on the risk of dementia in patients with RA could help one to better understand the role of CVD risk factors in the setting of chronic systemic inflammation in RA.

The third novel finding our study brings forth is the association of depression and anxiety with the incidence of dementia in patients with RA. Patients with RA are more likely to suffer from depression and anxiety than the general population as a result of their chronic illness manifesting as pain and functional disability.[41] In the general population, the association between depression and dementia has been linked to "vascular depression dementia hypothesis" and chronic inflammation.[25] The pathway from vascular disease to depression and then toward dementia

is perhaps not sequential. Studies have shown that depression and vascular disease are interrelated and can precipitate the risk of each other.[42] The interplay (ie, interaction and/or mediation of effect) between chronic inflammation, vascular disease, and depression may lead to increased risk of dementia.[25] Whether the association between depression and anxiety with dementia in RA indirectly reflects the effect of RA disease or is explained by other mechanisms (eg, poor sleep, impaired coping, and social isolation in patients with depression) remains to be established in future studies.

The evidence on the association between the use of RA medications and the risk of dementia is somewhat contradictory. Several previous studies reported conflicting results of MTX being beneficial as well as being associated with risk for dementia.[43-45] Two previous studies from the United States and the United Kingdom showed a reduced risk of dementia with the use of biologics in patients with RA.[46,47] A previous large cohort study using propensity score matching did not find any difference in the risk of dementia in patients with RA treated with a TNFi, IL-6 inhibitor, or Janus kinase inhibitor vs abatacept, although patients were followed up for a maximum of only 3 years.[48] In our study, we did not find an association between exposure to DMARDs at any time during the follow-up (ie, ever use) and incident dementia. Evaluating effects of medications on outcomes using the definitions of ever use or current use is problematic and introduces a possibility of confounding by indication/contraindication and channeling bias. This precludes firm conclusions about the effects of antirheumatic medications on dementia in observational studies like ours. Randomized interventional studies and observational studies using propensity score matching and extended follow-up can help better understand the association between DMARD use and dementia risk in RA.

Our study has important clinical implications. We have defined features of a high-risk phenotype for dementia incidence among patients with RA. An elderly patient with RA who has high disease activity, an unfavorable CVD risk profile, and/or a mood disorder is at high risk for dementia. Awareness of these risk factors among clinicians caring for patients with RA, vigilant screening, and appropriately addressing these risk factors may help improve cognitive outcomes in patients with RA.

This study has several strengths, including the use of a population-based cohort of patients with incident RA with long and complete follow-up. Because dementia has a decades-long preclinical period, studies with short follow-up may not provide information on early risk factors. Thus, the longitudinal study design and comprehensive information on multiple important risk factors for dementia, available through the REP, uniquely strengthen our study.

The following limitations should be considered when interpreting our study. First, the population of Olmsted and surrounding counties in Minnesota is approximately 90% White, suggesting that the results of our study may not be generalizable to other, more racially diverse, populations. Second, inherent to the retrospective nature of the study, we relied on information available from medical records. While we had comprehensive data on several important risk factors, information on APO-ε4 carrier status, alcohol consumption, physical activity, use of over-the-counter anticholinergics and opioids, sleep, and comprehensive disease activity scores were not available. Third, we used one code-based definition of dementia; thus, misclassification of dementia cases cannot be completely ruled out. However, we believe that the following elements of the study design help to minimize this limitation: (1) patients were scrutinized for their comorbidities in a similar way during their regular rheumatology follow-ups and through their referrals to other specialties including neurology, and (2) regular follow-ups with rheumatology decrease the likelihood of leaving a chronic condition such as dementia undiagnosed. Fourth, at the time of inclusion into the study, we did not have information on patients who had MCI, which some patients may have had. This should be considered when interpreting the study findings. Finally, we evaluated risk factors for dementia overall but did not assess the risk for dementia subtypes. As AD is the predominant subtype of dementia, the results are primarily reflective of the risk associated with this subtype.

In summary, clinically active RA, HTN, CVD events, depression, and anxiety were associated with an elevated risk of dementia among patients with RA. Among CVD events, ischemic stroke and HF were most strongly associated with risk of dementia. These findings establish a high-risk phenotype for dementia incidence among patients with RA.

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