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Rheumatoid Arthritis, Cognitive Impairment, and Neuroimaging Biomarkers: Results from the Mayo Clinic Study of Aging

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Abstract.
Background: Observational studies suggested that dementia risk in patients with rheumatoid arthritis (RA) is higher than in the general population.
Objective: To examine the associations of RA with cognitive decline and dementia, and neuroimaging biomarkers of aging, Alzheimer's disease, and vascular pathology in adult participants in the Mayo Clinic Study of Aging (MCSA).
Methods: Participants with RA were matched 1:3 on age, sex, education, and baseline cognitive diagnosis to participants without RA. RA cases with MRI were also matched with non-cases with available MRI. All available imaging studies (i.e., amyloid and FDG PET, sMRI, and FLAIR) were included. The study included 104 participants with RA and 312 without RA (mean age (standard deviation, SD) 75.0 (10.4) years, 33% male and average follow-up (SD) 4.2 (3.8) years).
Results: Groups were similar in cognitive decline and risk of incident dementia. Among participants with neuroimaging, participants with RA ($n = 33$) and without RA ($n = 98$) had similar amyloid burden and neurodegeneration measures, including regions sensitive to aging and dementia, but greater mean white matter hyperintensity volume relative to the total intracranial volume (mean (SD)%: 1.12 (0.57)% versus 0.76 (0.69)% of TIV, $p = 0.01$), and had higher mean (SD) number of cortical infarctions (0.24 (0.44) versus 0.05 (0.33), $p = 0.02$).
Conclusion: Although cognitive decline and dementia risk were similar in participants with and without RA, participants with RA had more abnormal cerebrovascular pathology on neuroimaging. Future studies should examine the mechanisms underlying these changes and potential implications for prognostication and prevention of cognitive decline in RA.

Keywords: Cognitive decline, cognitive impairment, dementia, magnetic resonance imaging, rheumatoid arthritis

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INTRODUCTION

Growing evidence from observational studies suggests that the risk of cognitive impairment and dementia in patients with rheumatoid arthritis (RA) and other autoimmune rheumatic conditions is higher than in the general population [1–5]; however, not all studies agree [6, 7]. Differences in study designs and study populations (e.g., clinic-based versus population-based studies) could account for some of the differences in study findings [6].

RA disease activity and increased levels of pro-inflammatory cytokines have been associated with cognitive impairment [8, 9], suggesting that the systemic inflammation that characterizes RA may accelerate the commencement and evolution of cognitive decline and dementia. In addition, several rheumatic diseases, including RA, are associated with increased risk of cardiovascular disease (CVD), cerebrovascular accidents (CVA) [10], and silent vascular damage, resulting in cerebrovascular and neurodegenerative changes and cognitive decline [11]. Chronic pain, depression, anxiety, the use of antidepressants and analgesics are common in patients with RA and could have potentially detrimental effects on cognitive function [12, 13]. The role of disease-modifying antirheumatic drugs (DMARDs) such as methotrexate and tumor necrosis factor-α (TNF-α) inhibitors on cognitive function in RA is controversial with several observational studies showing reduced risk of dementia [14, 15], while some report no benefit [2, 16]. Thus, the association between RA and cognitive impairment is multifactorial and could be due to chronic systemic inflammation, medication use and adverse CVD/CVA risk profile in patients with RA [17].

This study aimed to examine the associations between RA, cognitive decline and impairment, and neuroimaging biomarkers of dementia, aging, and vascular pathology [using PiB and FDG- positron-emission tomography imaging (PET), structural and fluid-attenuated inversion recovery (FLAIR) magnetic resonance imaging (MRI)] among the participants of the Mayo Clinic Study of Aging (MCSA).

MATERIALS AND METHODS

Mayo clinic study of aging

The MCSA is a population-based study of cognitive aging, mild cognitive impairment (MCI), and dementia. MCSA is an age and sex-stratified random sample of community-dwelling Olmsted County (MN) residents initiated in 2004 [18]. Initially, Olmsted County (MN) residents aged 70 to 89 years on October 1, 2004, were enumerated using the Rochester Epidemiology Project (REP) medical records–linkage system [19] and selected using an age-stratified and sex-stratified random sampling scheme. Exclusion criteria included terminal illness, hospice care, or dementia diagnosis. In 2012 and 2015, recruitment expanded to 50–69-year-olds and 30–49-year-olds, respectively. Recruitment of persons with dementia started in 2014. Participants are invited for follow-up visits every 15 months, following the same baseline evaluation protocol. Trained nurses review participants' medical records to abstract data on chronic conditions, such as diabetes, hypertension, dyslipidemia, coronary artery disease, atrial fibrillation, congestive heart failure, stroke, and depression.

At each visit, a study coordinator collected sociodemographic factors, asked questions on memory, activities of daily living, and neuropsychiatric symptoms. A physician administered the Short Test of Mental Status [20], reviewed the medical history, and performed a neurological examination. Nine neuropsychological tests, administered by a psychometrist, were used to assess cognitive performance in four domains [18]: 1) memory (AVLT Delayed Recall [21], WMS-R Logical Memory II, and Visual Reproduction II) [22]; 2) language (Boston Naming Test [23], Category Fluency [24]); 3) attention/executive (Trail Making Test B [24, 25], WAIS-R Digit Symbol [26]); 4) visuospatial (WAIS-R Picture Completion & Block Design [26]). The psychometrists were unaware of the study aims, RA diagnosis or clinical characteristics that cannot be observed at a visit. Cognitive performance, for each participant, in each cognitive domain was compared with age-adjusted scores of individuals previously obtained using Mayo's Older American Normative Studies [27–29].

After reviewing each participant's information, the final diagnosis (i.e., cognitively unimpaired (CU), MCI, dementia) at each MCSA visit was adjudicated by consensus between the study coordinator, the physician, and a neuropsychologist. The MCI criteria were described previously [30] and are as follows: 1) cognitive concern by a physician, the participant or study partner, 2) impairment in one or more cognitive domain, 3) essentially normal functional activities, and 4) absence of dementia. Individuals were diagnosed with dementia if they met the Diagnostic and

Table 1
Demographic characteristics and comorbidities of patients with RA and their comparators matched on age, sex, education, and MCSA baseline cognitive diagnosis

Characteristics	with RA (N = 104)	without RA (N = 312)	*p*
Age at baseline visit (y), mean (SD)	75.0 (10.5)	75.0 (10.4)	*
Sex, male	34 (33)	102 (33)	*
Education (y), mean (SD)	13.8 (2.2)	13.8 (2.2)	*
Cognitive status at baseline visit			*
Cognitively unimpaired	80 (77)	240 (77)	
Mild cognitive impairment	21 (20)	63 (20)	
Dementia	3 (3)	9 (3)	
Apolipoprotein E ε4 carrier	27 (26)	95 (30)	0.46[1]
Global cognitive z-score, mean (SD)	–0.03 (1.04)$^{\{95\}}$	0.00 (1.01)$^{\{287\}}$	0.90[2]
Years, from first to last visit, mean (SD)	3.9 (3.4)	4.3 (3.9)	0.56[2]
Number of visits, mean (SD)	3.8 (2.6)	4.2 (3.0)	0.43[3]
History of sleep apnea	18 (17.3)	36 (11.5)	0.13[1]
History of depression	56 (55)$^{\{102\}}$	116 (37)	0.002[1]
History of hypertension	80 (78)$^{\{102\}}$	226 (72)	0.25[1]
History of diabetes	21 (21)$^{\{102\}}$	51 (16)	0.37[1]
History of coronary artery disease	34 (33)$^{\{102\}}$	90 (29)	0.39[1]
History of congestive heart failure	15 (15)$^{\{102\}}$	25 (8)	0.054[1]
History of atrial fibrillation	13 (13)$^{\{102\}}$	42 (13)	1.00[1]
History of stroke	4 (4)$^{\{102\}}$	20 (6)	0.47[1]
Body mass index, kg/m^2, median (IQR)	27.1 (23.8, 31.4)$^{\{99\}}$	27.7 (25.4, 31.8)$^{\{305\}}$	0.13[2]

N (%) unless otherwise stated; {N}, number of participants; MCSA, Mayo Clinic Study of Aging; RA, rheumatoid arthritis; SD, standard deviation; IQR, interquartile range. *matching variables; [1]Fisher's exact test; [2]Kruskal-Wallis rank sum test; [3]Pearson's Chi-squared test.

Statistical Manual of Mental Disorders-IV (DSM-IV) criteria for dementia [31]. Evaluators were blind to any previous cognitive diagnosis. Individuals who performed in the normal range and did not meet the criteria for MCI [30] or dementia [31] were classified as CU. An extensive medical record review, using the REP resources, occurs every five years for participants lost to follow-up to ascertain dementia when they reach 70 years of age. In the present study population, there was no difference between the two groups (with and without RA) in the proportion of participants with the additional medical record review. The REP medical records linkage system captures the medical information for all Olmsted County residents who received care in the county; more than 90% of persons aged 70 and older return for a visit at least once within 1 year [19]. This allows excellent ascertainment of medical conditions over time.

In MCSA, participants are also given the opportunity to undergo neuroimaging studies to assess dementia-related neuroimaging biomarkers, including global amyloid-β (Aβ) using PiB- PET, neurodegeneration (hypometabolism via FDG-PET, hippocampal volume, and cortical thickness via sMRI), and cerebrovascular pathology using FLAIR MRI (white matter hyperintensity [WMH] burden, subcortical, and cortical infarctions). In addition, Apolipoprotein E (*APOE*) ε4 status was determined from blood draw at MCSA baseline assessment.

Study population

The present study, designed in fall of 2020, included MCSA participants diagnosed with RA prior to their MCSA baseline visit between January 2005 and January 2020; those diagnosed with RA after the MCSA baseline visit were excluded. Each participant with RA was matched 1:3 to MCSA participants without RA on age at MCSA baseline visit, sex, years of education, and MCSA baseline cognitive diagnosis (i.e., CU, MCI, or dementia). There were 80 CU participants at baseline with RA (matched with 240 CU MCSA participants without RA), 21 participants had RA and MCI (matched with 63 MCSA participants with MCI but without RA), and 3 participants had RA and dementia (matched with 9 MCSA participants with dementia but without RA) (Table 1). The study sample was determined by the availability of the RA diagnosis in MCSA participants and was not determined in advance by the investigators.

MCSA participants with RA were part of a population-based RA cohort [32, 33] that captured all incident and prevalent cases of RA between 2005

and 2020. MCSA evaluators were not aware of the study aims, participants' RA diagnosis, and all evaluations were blind to the RA diagnosis. Likewise, the present study's investigators were unaware of the RA patients' cognitive performance. Investigators had access but did not focus on each individuals' cognitive performance. Cognitive performance measures were aggregated in table summaries at the time of analysis.

MCSA participants with RA and available MRI were matched to non-cases 1:3 on age at MCSA baseline visit, sex, education, cognitive status at MCSA baseline, and having undergone at least one MRI. We used the first MRI available for the RA cases and selected participants without RA with available MRI at MCSA baseline. The cognitive status of the RA cases did not change until they underwent MRI. RA cases who underwent neuroimaging and their matches were included in the analyses examining the association of RA with neuroimaging biomarkers of AD and vascular pathology. We were unable to identify a third match for one of the participants with RA and decided to leave the groups imbalanced rather than modifying the matching criteria.

Standard protocol approvals, registrations, and patient consents

Study protocols were approved by the Institutional Review Boards of the Mayo Clinic and the Olmsted Medical Center, and participants provided written informed consent before participation. In the case of participants with cognitive impairment sufficient to interfere with capacity, consent was obtained from a legally authorized representative.

RA characteristics

All participants with RA met the 1987 and/or 2010 American College of Rheumatology (ACR) classification criteria for RA [34, 35] or were prevalent cases identified based on physician diagnosis of RA. Data on erythrocyte sedimentation rate (ESR) were available from the medical records. Information on conventional synthetic (csDMARDs) and biologic disease-modifying antirheumatic drugs (bDMARDs), i.e., TNF-α inhibitors (TNFi) and non-TNFi biologics, were manually abstracted from medical records by trained nurse abstractors. "Other csDMARDs" included leflunomide, sulfasalazine, azathioprine, gold, d-penicillamine, cyclosporine, and cyclophosphamide. "Seropositivity" was defined as positivity for either rheumatoid factor (RF) and/or anti-cyclic citrullinated peptide antibody (anti-CCP) at any time.

Neuroimaging measures

Amyloid PET

Details are presented previously [36]. Amyloid PET imaging was performed with ^{11}C-Pittsburgh Compound B (PIB) [37, 38]. The amyloid PET target meta-regions of interest (ROI) included the prefrontal, orbitofrontal, parietal, temporal, anterior, and posterior cingulate and precuneus ROIs, referenced to the cerebellar gray crus region. The cut point for elevated amyloid PET was a standardized uptake value ratio (SUVR) value >1.48 (centiloid 22) [38] to assign participants as Aβ positive [36, 39].

FDG-PET

Details on the acquisition, processing, and summary measure have been reported previously [40]. FDG-PET images were obtained 30–40 min after tracer injection (fluorodeoxyglucose (^{18}F-FDG)). A computed tomography image was obtained for attenuation correction. An AD signature FDG PET composite was calculated based on glucose metabolic rates from an AD signature meta-ROI and consisted of the average bilateral angular gyri, posterior cingulate, and inferior temporal cortical ROIs normalized to pons and vermis uptake [40].

MRI

All MRI images were acquired on 3 T GE MRI (GE Medical Systems, Milwaukee, WI). The neurodegeneration MRI measure was a FreeSurfer (version 5.3)-derived temporal meta-ROI cortical thickness, composed of the surface-area weighted average of the mean cortical thickness in the individual ROIs: entorhinal cortex, fusiform, inferior temporal, and middle temporal [36]. Reduced temporal meta-ROI cortical thickness was defined as $\leq$2.68 mm [36, 39]. The FreeSurfer processing failed in one study participant.

Vascular neuroimaging biomarker acquisition has been described previously [41]. Briefly, WMH images on standard two-dimensional T2 FLAIR were segmented and edited by a trained imaging analyst using a semiautomated method. WMH was scaled by total intracranial volume (TIV). A cut point of 1.7% WMH of TIV was chosen to identify the individu-

als with abnormal WMH levels. Cortical infarctions were identified on the T2 FLAIR sequence, with a corresponding T1 hypointensity required for confirmation. They were characterized as hyperintense T2 FLAIR lesions (gliosis) involving cortical gray matter that extended to the cortical edge with or without the involvement of the underlying white matter [41]. Subcortical infarctions were characterized as hyperintense T2 FLAIR lesions with a dark center, seen in the white matter, infratentorial, and central gray-capsular regions. The dark area (tissue loss) was greater than or equal to 3 mm in diameter as measured on the T2 FLAIR or T1 (whichever image shows the findings more clearly) [41].

Statistical analysis

Participants' characteristics were summarized using descriptive statistics (mean, standard deviation, median, interquartile range, count, percentage) and compared between groups using Pearson's Chi-squared, Fisher's exact or Kruskal-Wallis tests as appropriate. For the analyses, the raw neuropsychological tests' scores in each cognitive domains were z-scored and averaged to calculate domain-specific cognitive z scores (i.e., memory, language, attention/executive, and visuospatial skills) and a global cognitive z-score (i.e., for overall cognitive performance) was calculated by averaging the four domain-specific z-scores.

The association of RA and its activity markers with progression to dementia in participants without dementia at MCSA baseline was examined using Cox proportional hazards models adjusted for age, sex, education (years), and MCSA baseline cognitive status. Similarly, a Cox proportional hazards model adjusting for age, sex, and education was used to compare progression to dementia among RA and non-RA CU participants.

We also examined the association of RA and its characteristics, comorbidities, and markers of RA activity (exposure variables) with change in global cognitive z-score, using linear mixed-effects models. Specifically, among participants without dementia at study baseline, the association was examined using a linear mixed-effects model adjusted for age, sex, education, baseline cognitive diagnosis, and whether the administration of the cognitive tests was the first time ever (i.e., test naïve), allowing for random subject-specific intercepts and slopes. A linear mixed-effects model adjusting for age, sex, education, and test naïve status was used to examine the association between exposure variables and change in global cognitive z-score among CU participants at study baseline. Estimated coefficients and standard errors are presented.

Analyses were considered statistically significant at a p-value <0.05 and were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC) and R 4.0.3 (R Foundation for Statistical Computing).

RESULTS

The overall analysis cohort comprised 104 participants with RA and 312 matched participants without RA. Among the 104 participants with RA, 80 were CU, 21 with MCI, and 3 with dementia at study baseline; their characteristics and their matched non-RA participants' characteristics are presented in Table 1. As expected, participants with versus without RA did not differ in age, sex, years of education, or baseline cognitive status as these were the matching characteristics for the two groups. There was no difference in the follow-up time [from first to last visit; (mean (SD)) for participants with RA was 3.9 (3.4) years and for participants without RA was 4.3 (3.9) years ($p = 0.56$)] or the number of visits. Study participants were primarily white (97% in those with RA and 99% in those without RA) and not Hispanic or Latino (99%). There was no evidence of a significant difference between the two groups in APOE $\varepsilon 4$ carrier status (yes/no) or major CVD comorbidities.

RA and neuroimaging biomarkers

Thirty-three participants with RA cases had undergone neuroimaging (i.e., MRI) and were matched with non-cases that had undergone at least one MRI. RA cases with and without neuroimaging did not have statistically significant differences in age, sex, years of education, RA activity markers, cognitive status at last follow-up (visit or medical record review) or treatment characteristics (Table 2). Although RA cases were more likely to have diabetes, they had a similar otherwise comorbidity profile compared to matched non-cases.

In participants with available neuroimaging biomarkers, we did not observe a statistically significant difference in Aβ burden and neurodegeneration measures, including regions sensitive to aging and dementia, between RA participants and their matched comparators (Table 2). However, participants with RA (versus without RA) had greater mean WMH vol-

Table 2
Characteristics of patients with RA and their comparators matched on age, sex, education, MCSA baseline cognitive diagnosis, and MRI availability

Characteristics	With RA ($n=33$)	Without RA ($n=98$)	p[1]
Age (y), mean (SD)	76.2 (8.0)	75.7 (8.0)	0.79
Sex, male	12 (36)	34 (35)	1.00
Education (y), mean (SD)	14.3 (2.3)	14.2 (2.3)	0.73
Cognitive diagnosis at MCSA baseline and MRI			0.91
Cognitively unimpaired	25 (76)	77 (79)	
Mild cognitive impairment	7 (21)	18 (18)	
Dementia	1 (3)	3 (3)	
Diagnosis at last follow-up (visit or medical record review)			0.26
Cognitively unimpaired	17 (52)	64 (65)	
Mild cognitive impairment	5 (15)	15 (15)	
Dementia	11 (33)	19 (19)	
Apolipoprotein E ε4 carrier	6 (18)	26 (27)	0.48
Body mass index, kg/m², median (IQR)	26.5 (23.8, 28.7)	27.3 (24.0, 29.4){97}	0.42
History of depression	14 (42)	41 (42)	1.00
History of hypertension	26 (79)	70 (71)	0.50
History of diabetes	6 (18)	5 (5)	0.03
History of coronary artery disease	7 (21)	22 (22)	1.00
History of congestive heart failure	4 (12)	7 (7)	0.47
History of atrial fibrillation	1 (3)	14 (14)	0.11
History of stroke	1 (3)	4 (4)	1.00
Neuroimaging biomarkers[2]			
WMH volume % TIV, mean (SD)	1.12 (0.57)	0.76 (0.69)	0.01
Cortical infarctions, mean (SD)	0.24 (0.44)	0.05 (0.33)	0.02
Cortical thickness, mean (SD)	2.62 (0.16)	2.64 (0.15)	0.73
FDG SUVR, mean (SD)	1.51 (0.16)	1.59 (0.18)	0.46
Amyloid PET SUVR, mean (SD)	1.54 (0.40)	1.52 (0.33)	0.75

N (%) unless otherwise stated; N, number of participants; MCSA, Mayo Clinic Study of Aging; SD, standard deviation; IQR, interquartile range; RA, rheumatoid arthritis; FDG SUVR, fluorodeoxyglucose (^{18}F-FDG) standardized uptake value ratio; WMH, white matter hyperintensities; TIV, total intracranial volume. [1]Kruskal-Wallis rank sum test for continuous data and Fisher's exact test for categorical data. [2]49 participants (14 RA / 35 non-RA) had WMH burden data, 54 (17 RA / 37 non-RA) cortical infarctions, 130 (33 RA / 97 non-RA) cortical thickness, 45 (10 RA / 35 non-RA) FDG PET, and 47 (12 RA / 35 non-RA) Amyloid PET data.

ume relative to the TIV (mean (SD)%: 1.12 (0.57)% versus 0.76 (0.69)% of TIV, $p=0.01$) and had a higher mean (SD) number of cortical infarctions (0.24 (0.44) versus 0.05 (0.33) ($p=0.02$) (Table 2). These associations persisted when the comparisons were limited to CU participants (not shown in tables). In addition, these associations persisted when participants with diabetes (i.e., a potential risk factor for WMH) [42] were excluded [WMH volume % TIV, mean (SD) in participants with RA versus without RA: 1.21 (0.60)% versus 0.66 (0.56)% of TIV, $p=0.003$).

RA, cognitive decline, and dementia risk

Participants with RA and cognitive impairment at MCSA baseline were older, more likely to be men, with fewer years of education on average and borderline longer RA duration (Table 3). Participants with and without RA did not differ in their risk of incident dementia (Table 4). However, in participants with RA, there was a marginally insignificant increase in the risk of incident dementia for every year increase of RA duration (per year increase of RA duration, HR = 1.04, 95%CI (1.0, 1.1), $p=0.07$; Supplementary Table 1).

As Table 5 presents, the coefficient for time indicates that each one-year increase in time is associated with a decline in global cognitive z-score of 0.05 (95% CI: –0.06, –0.04) for CU without RA and with a decline of 0.03 (i.e., –0.05+0.02; 95% CI: –0.05, –0.01) in CU with RA. Thus, the decline in global cognitive z-score is less steep in RA participants. The difference in slope estimates (i.e., annualized change from baseline) reached statistical significance ($p=0.023$), but this difference was small, and its clinical significance is uncertain.

Among CU participants with RA, a steeper annual change in global cognitive z-score was observed in participants with diabetes (versus no diabetes; i.e.,

Table 3
Disease activity and treatment characteristics between RA cases with and without cognitive impairment at the Mayo Clinic Study of Aging baseline

	CU (N = 80)	MCI/Dementia (N = 24)	Total (N = 104)	*p*
Age at baseline visit (y), Mean (SD)	74 (11)	80 (7)	75 (10)	0.018[1]
Sex, male	20 (25)	14 (58)	34 (33)	0.005[2]
Education (y), mean (SD)	14 (2)	13 (2)	14 (2)	0.049[1]
RA duration (y), mean (SD)[3]	15 (11)	22 (17)	17 (13)	0.09[1]
RF or anti-CCP positive[4]	48 (69){70}	11 (79){14}	59 (70){84}	0.54[2]
ESR at RA diagnosis, mm/h, mean (SD)	20 (17){58}	18 (12){15}	20 (16){73}	0.92[1]
Max ESR first year, mm/h, mean (SD)	27 (22){56}	22 (15){14}	26 (21){70}	0.89[1]
ESR at baseline visit, mm/h, mean (SD)	16 (16){47}	16 (16){13}	16 (16){66}	0.73[1]
Methotrexate use[5]	44 (55)	13 (54)	57 (55)	1.00[2]
Hydroxychloroquine use[5]	32 (40)	12 (50)	44 (42)	0.48[2]
Biologic DMARDs use[5,6]	19 (24)	5 (21)	24 (23)	1.00[2]
Other csDMARDs use[5,7]	22 (28)	3 (12)	25 (24)	0.18[2]

N (%) unless otherwise stated; {N}, number of participants; SD, standard deviation; RA, rheumatoid arthritis; RF, rheumatoid factor; ESR, erythrocyte sedimentation rate; DMARD, disease-modifying anti-rheumatic drug. [1]Kruskal-Wallis rank sum test; [2]Fisher's exact test; [3]RA duration is defined as time from RA diagnosis to Mayo Clinic Study of Aging baseline; [4]Positivity for either rheumatoid factor (RF) or anti-cyclic citrullinated peptide antibody (anti-CCP) at any time; 20 missing (10 in CU and 10 in MCI/dementia group); [5]Prior to MCSA baseline; [6]Any bDMARD (including tumor necrosis factor alpha inhibitors); [7]Leflunomide, sulfasalazine, azathioprine, gold, d-penicillamine, cyclosporine, and cyclophosphamide.

Table 4
The association of RA with incident dementia

Comparison groups	Outcome: Incident dementia				
	N	Events	HR	95%(CI)	*p*
			In CU/MCI, study baseline		
RA versus non-RA (Ref)[1]	404	66	0.96	0.5, 1.7	0.90
			In CU, study baseline		
RA versus non-RA (Ref)[2]	320	35	1.0	0.4, 2.3	1.00

RA, rheumatoid arthritis; N, number of participants; HR, hazard ratio; CI, confidence interval. [1]Hazard Ratio (95% Confidence Interval) retained from Cox Proportional Hazards Models for Incident Dem-MR review adjusted for age, sex, education, and baseline cognitive status (CU/MCI). [2]Hazard Ratio (95% Confidence Interval) retained from Cox Proportional Hazards Models for Incident Dem-MR review adjusted for age, sex, and education.

Table 5
Association between RA and change in global cognitive z-score from MCSA baseline

RA versus without RA	Global cognitive z-score		
	Coefficient	SE	*p*
	Without dementia (study baseline)[1]		
RA	–0.05	0.08	0.572
Time	–0.05	0.004	<0.001
RA*time	0.01	0.009	0.138
	CU (study baseline)[2]		
RA	–0.08	0.09	0.380
Time	–0.05	0.004	<0.001
RA*time	0.02	0.009	0.023

RA, rheumatoid arthritis; MCSA, Mayo Clinic Study of Aging; CU, cognitively unimpaired; SE, standard error. Fixed model results from a linear mixed effects model allowing for random individual intercepts and slopes; slope estimates represent an annualized change from baseline. [1]Model includes RA, time, and RA*time interaction and controls for age at baseline visit, sex, education, baseline cognitive diagnosis (MCI versus CU), and test naïve. [2]Model includes RA, time, and RA*time interaction and controls for age at baseline visit, sex, education, and whether the administration of the cognitive tests was the first time ever (i.e., test naïve).

an annual decline from baseline of (–0.02 +(–0.06)) z-scores) (Supplementary Table 2). Participants who received prior bDMARDs (or TNFi) treatment did not present any appreciable change in global cognitive z-scores during the follow-up (versus no bDMARDs; i.e., an annual increase from baseline of -0.03 +0.05 z-scores). However, these changes were small, and possibly imprecise due to the small sample size and any clinical significance is uncertain.

DISCUSSION

The risk for incident dementia was similar in participants with RA versus matched comparators without RA. The decline in global cognitive z-score was less steep in CU participants with RA (versus CU without RA), but this difference was small, and its clinical significance is uncertain. In participants with RA, a longer disease duration had a marginally insignificant association with an increased risk of dementia. Of note, there was no detectable cognitive decline in participants with RA who received TNFi in the past (versus no TNFi) or any bDMARDs (versus no bDMARDs). Although the study sample size was small, we were able to observe that participants with RA (versus without RA) had more abnormalities in neuroimaging measures of cerebrovascular pathology. The two groups did not have significant differences in their sociodemographic characteristics, APOE $\varepsilon 4$ status, cognitive status at baseline, neurodegeneration imaging biomarkers and most comorbidities, except diabetes that was more frequent in RA cases.

Previous studies present mixed findings, reporting either no association [6] or decreased cognitive performance in RA versus the general population [1]. The cross-sectional design of several previous studies makes it difficult to understand any contributing role of RA in the commencement and progression of cognitive decline, especially given the long latency between pathophysiological brain changes and dementia clinical symptoms. MCSA prospectively recruited and cognitively evaluated participants, and we observed that overall, there was no difference in dementia risk between patients with RA (versus matched comparators). However, patients with less severe RA could have been more likely to participate (versus more severe cases), thereby biasing the overall risk estimate towards the null. In addition, a longer RA duration had a marginally insignificant association with an increased risk of dementia. This could imply that patients with more recent RA onset (thus shorter RA duration) benefitted from more effective treatments (bDMARDs); or that regardless of the availability of treatments, cumulative extended exposure to imperfectly controlled underlying inflammation might increase the risk of dementia, or both. Our previous work [33], using a retrospective population-based cohort study, observed an increased risk of dementia in patients diagnosed with RA in the 1980 s and 1990 s (versus non-RA cohorts), and a subsequent decreased risk in the 2000 s; such decrease in risk coincided with the arrival of novel biologic treatments (bDMARDs) for RA.

In the present study, participants with RA and diabetes had a significantly steeper cognitive decline compared with RA participants without diabetes, which is in agreement with previous research suggesting that diabetes is a risk factor of cognitive impairment [43].

Findings also suggest that participants with RA, who received bDMARDs (including TNFi) did not have decline in their global cognitive z-score during the follow-up; an important observation regarding cognitive changes in the chronic inflammatory setting of RA and the use of bDMARDs. While these findings may suggest a potential benefit of bDMARDs in impeding cognitive decline, the sample size was small, and cautious interpretation of the results is warranted. In addition, each patient with RA could have received multiple different medications for which models did not adjust for. Previous reports on the association between RA medications and cognitive impairment have been mixed. Studies have suggested a protective effect of antirheumatic medications on the risk of dementia in patients with RA, either using csDMARDs (e.g., methotrexate) or bDMARDs [14, 15, 44–46]. In addition, adalimumab (a TNFi) has been shown to improve cognitive impairment and neuroinflammation in a mouse AD model [47] and a vascular dementia model [48]. However, not all studies agree, showing no association [49], or an increased risk of vascular dementia, but not AD, in RA patients using csDMARDs [16], or mixed findings in observational studies with etanercept (TNFi) [2, 16] in patients with RA. We cannot exclude that part of these conflicting findings from observational studies could be due to confounding by indication when patients with more severe RA, higher inflammatory burden, and potentially higher baseline probability of developing dementia are more likely

to be prescribed bDMARDs than those with milder RA. The extent to which cognitive impairment and dementia in RA can be prevented and/or ameliorated by modifying autoimmune and/or inflammatory activity is not well understood and is a critical barrier to improving outcomes.

Study findings also suggest more abnormalities in cerebrovascular imaging biomarkers in participants with RA, despite a mostly similar CVD comorbidity profile except for diabetes reflecting a higher burden of subclinical, silent CV abnormalities in RA. Similar findings were supported even when participants with diabetes were excluded. Patients with RA have a known higher CVD risk which has been largely attributed to CV risk factors, chronic inflammation, and antirheumatic medication toxicity [11]. It should also be noted that the study looked at neurodegeneration biomarkers including regions sensitive to aging and dementia (especially AD dementia). We cannot exclude that focusing on other brain regions (or other biomarkers) the observed associations could be different and could also provide insightful information for cognitive impairment pathways in patients with the specific underlying pathophysiological mechanisms of rheumatic diseases.

Studies on neuroimaging biomarkers in patients with RA are limited, and our findings are novel. Brain damage from stroke and silent vascular damage such as WMHs, increases in autoimmune rheumatic diseases (including RA) [50]. Plasma markers of inflammation (e.g., C-reactive protein, TNF-α, interleukin-6) are also associated with stroke and increased WMH burden [50]; thus, RA inflammation could be partly positively associated with cerebrovascular imaging biomarkers. Previous studies suggest that WMH burden and brain infarcts are associated with a higher risk for dementia (including AD), stroke, and death [51]. In addition, WMH changes over time could significantly predict cognitive decline [52], emphasizing the potential clinical significance of MRI cerebrovascular biomarkers; thus, future, more extensive longitudinal studies are warranted in patients with RA.

Study findings need to be interpreted considering the study's strengths and limitations. Study strengths include the serial comprehensive cognitive evaluations and diagnosis, blind to any previous clinical diagnosis, following the same protocol in all visits, and availability of other than RA chronic medical conditions information. In addition, a significant strength of the study is the availability of multiple, reliable measures of brain pathophysiology (i.e., neuroimaging biomarkers) assessed by multimodal, state-of-the-art imaging. On the other hand, sample size was small, and even more reduced in the analysis with neuroimaging biomarkers. In addition, if patients with less severe RA were more likely to participate in the study than those with severe RA, dementia risk estimates might have been biased toward the null (assuming RA is positively associated with dementia). We were not able to control for additional potential confounders that were not addressed in the present study (e.g., pain, physical activity). Understanding the association between cumulative RA disease activity, functional status and cognition in RA is a subject for our future studies. Similar neuroimaging findings were supported when participants with diabetes were excluded; however, we cannot exclude that diabetes could partially explain the neuroimaging abnormalities. Although there was no difference between the two groups (with and without RA) in the proportion of participants with the additional medical record review for dementia, we cannot preclude that those participants with more severe RA activity or more severe cognitive impairment would be more likely to drop-off the active follow-up and miss the neuropsychological test assessment; however, the medical record review for dementia diagnosis helps to minimize bias due to lost-to-follow-up in the hazard models estimation. In addition, a much longer follow-up time would be needed to see the impact of vascular neuroimaging biomarkers on cognition.

In conclusion, the risk for incident dementia was similar in participants with RA versus matched on age, sex, years of education, and MCSA baseline cognitive diagnosis non-RA comparators. However, participants with RA had more abnormal cerebrovascular imaging biomarkers than participants without RA, even after excluding participants with diabetes. Participants with RA who were treated with bDMARDs had no cognitive decline during the follow-up. However, changes in cognitive decline observed in the study were subtle and additional studies are needed to examine these associations further and comprehend their clinical significance and potential value for prognosis and prevention of cognitive decline and dementia in RA patients. Further, more extensive studies would be valuable to our understanding and insight into developing interventions to prevent cerebrovascular pathology in patients with RA.

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SUPPLEMENTARY MATERIAL

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