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Letter

Clinically Active Rheumatoid Arthritis and the Presence of Cardiovascular Disease Are Associated With an Elevated Risk of Dementia Incidence

To the Editor:

We read with great interest the recent population-based cohort study by Kodishala and colleagues in *The Journal of Rheumatology* on risk factors for the development of dementia in patients with incident rheumatoid arthritis (RA).[1] The authors reached the conclusion that clinically active RA and the presence of cardiovascular (CV) disease are associated with an elevated risk of developing dementia incidence in patients with RA, in addition to age, hypertension, depression, and anxiety, which are universally recognized risk factors for dementia. We support and appreciate the authors' work and agree with the conclusions but have some concerns regarding certain details in the article.

First, the proportion of women with RA is higher than that of men. Epidemiological studies have shown that women have a higher risk, rate of decline, prevalence, and severity of Alzheimer disease (AD).[2] Thus, sex was indeed a confounding variable in this study. According to the cognitive reserve theory, education is crucial for understanding the risk of cognitive impairment in later life, as more educated individuals may maintain cognitive function for longer than less educated individuals, despite accumulating brain pathology during the aging process.[3] Studies have also shown that lower educational attainment contributes to an increased risk of developing RA.[4] Therefore, controlling for the confounding effects of education is necessary for the reliability of this study. The authors mention in the text that the population of Olmsted and surrounding counties in Minnesota is approximately 90% White.[1] Some studies have shown that, at least in the United States, the risk of cognitive impairment varies by race. For example, among noncarriers of the APOE-e4 allele, the risk of AD is 2.3 times higher in Black/African American than in White individuals.[5] Thus, racial differences are an important confounder as well as educational attainment. Therefore, we suggest that confounding factors, including at least age, education, sex, calendar year of RA incidence, and race, should be adjusted before refining the models (model 1 and model 2).[1] In addition, studies have shown that chronic pain is common in RA, and is associated with cognitive decline.[6] Therefore, although the authors included several indicators, the most common and important symptom for patients with RA—chronic pain—should be described in the text.

Second, the authors mention in the text that inflammatory markers (erythrocyte sedimentation rate [ESR] at RA incidence, highest ESR in the first year after RA incidence) were not related to an increased risk of dementia and explained that they may be related to the high variability of ESR. In addition, single timepoint inflammatory markers may not be a reliable indicator of cumulative inflammatory burden and its relationship with dementia. However, the mean of multiple measurements over the study period is more convincing than inflammatory markers assessed at a single timepoint. For example, multiple timepoints could be chosen for measurements, such as at baseline, at the midpoint of the study, and at the end of the study. Also, we did not obtain any information on RA disease activity scores (eg, Disease Activity Score in 28 joints, Clinical Disease Activity Index, Simplified Disease Index), which are more indicative of changes in inflammatory activity in patients with RA and are more representative than inflammatory markers at a single timepoint.

Finally, the authors assessed risk factors for dementia overall, but not for subtypes of dementia. Also, it is unclear whether information about dementia in terms of speech function, memory, and attention are different in people with RA, which may be more helpful to focus on for prevention and treatment of the subtypes of dementia mentioned above.[7] Information about personal characteristics, including CV disease and CV risk factors, was not updated over time. The homogeneous (eg, single racial/ethnic group) and small sample nature of this study limits its generalizability. Future results from large samples are needed to test the results of the trial.

We would again like to thank Kodishala and colleagues for their contributions to this field of study and look forward to hearing from them.

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