Drs. Deane and Demoruelle reply

To the Editor:

In the letter by Alpizar-Rodriguez and Finckh[1], they describe their prior work in which they found, similar to our current report, an association between older age and anticitrullinated protein antibody (ACPA) positivity in first-degree relatives (FDR) of patients with rheumatoid arthritis (RA)[2,3]. In contrast to our findings, their data suggest that the strongest association between ACPA positivity and age is in women aged 45–55 years, and they did not find an association between ACPA positivity and age in men. They also found that being postmenopausal was strongly associated with ACPA positivity in women. However, as they state in their letter, they did not have enough ACPA-positive men (n = 7) to definitively determine the presence or absence of an association between ACPA and age in men.

In our report, we had a larger number of ACPA-positive men (n = 13), and we were able to see an association between ACPA positivity and age in both men and women. Thus our data suggest that it is not menopause alone influencing the development of ACPA in older FDR. It is also of interest that prior studies demonstrating associations between age and other autoantibodies (e.g., antinuclear antibodies and rheumatoid factor) did not find significant sex differences[4]. That being said, we do agree with Alpizar-Rodriguez and Finckh that menopause and changes in sex hormone levels may contribute in some way to RA pathogenesis in a subset of patients with RA. We also think this should be an important area for future research, especially to address the issues of whether age and menopausal factors contribute to the development of preclinical ACPA or to the transition from ACPA positivity to inflammatory arthritis classifiable as RA.

Another important difference in our study is that we looked at individual IgA and IgG ACPA isotypes. We were therefore able to establish for the first time that the strongest association between ACPA positivity and older age was specifically for IgA-ACPA. This is in line with the prior study by Alpizar-Rodriguez and Finckh[2], in which they found that an IgA-containing ACPA assay [i.e., anti-CCP3.1 (IgG/IgA)] was significantly higher in individuals age > 55 years (RR 4.5, 95% CI 1.3–5.5), whereas 2 IgG-only containing ACPA assays (i.e., anti-CCP2 and anti-CCP3) were not (RR 4.1, 95% CI 0.4–37.5 and RR 1.1, 95% CI 0.3–3.7, respectively). Given the potentially different roles that isotypes may play in the biology of RA development, as well as findings that IgG ACPA are more predictive of future RA development[5], future studies of ACPA in RA development as related to age and menopause should consider individual ACPA isotypes.

Given the relationship between age and menopause, it can be difficult to completely disentangle the individual contributions of these 2 factors in epidemiologic studies. Mechanistic studies are needed to truly understand the individual influences of age and menopause on ACPA generation as well as other autoantibody systems and the development of RA. Importantly, understanding exactly how age and menopause contribute to RA pathogenesis may lead to novel pathways for RA prevention.

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