Response to: 'Increasing incidence of autoantibody-negative RA is replicated and is partly explained by an aging population' by Matthijssen *et al*

We thank Matthijssen and colleagues for their interest in our study on the epidemiology of rheumatoid arthritis (RA), where we have reported a significant increase in incidence of rheumatoid factor (RF)-negative RA and a decrease in RF-positive RA in 2005–2014 compared with previous decades.[1] Matthijssen *et al* have independently assessed the incidence of anticitrullinated peptide antibody (ACPA)-negative and ACPA-positive RA in the Leiden Early Arthritis Cohort. In concordance with our findings, they found increasing incidence of ACPA-negative RA but not ACPA-positive RA.[2] Further, Matthijssen *et al* proposed that ageing of the population can be an important contributor to these trends and estimated that the rate of increase of new ACPA-negative RA cases in the next 20 years will outpace that of ACPA-positive RA (11% vs 2% increase, respectively), thus substantially increasing the prevalence of ACPA-negative RA.

Taken together with our findings, these results strengthen the argument that the serological profile of RA is changing in recent years, and autoantibody-negative RA is becoming more common in the new millennium. These findings have broad implications for both clinical practice and research. First, autoantibody-negative RA is a more clinically challenging disease subset due to diagnostic uncertainty in early disease with multiple potential mimickers, and frequent difficulty with timely choice of effective treatment.[3] This highlights the need for increased awareness of autoantibody-negative RA among physicians, in order to facilitate timely rheumatology referral and initiation of treatment. Second, classification of RA based on RF and ACPA is conditional to the available and validated immunological assays, while the search for additional immunological and clinical subsets within autoantibody-negative RA continues.[4] Refining the understanding of pathophysiology and classification of RA disease beyond the current immunological disease markers may lead to improvement in RA diagnosis and management, opening new avenues for individualised treatment selection for different RA subtypes.

Elena Myasoedova ,[1] **John Davis**,[1] **Eric L Matteson**,[1] **Cynthia S Crowson** [1,2]

[1]Rheumatology, Mayo Clinic, Rochester, Minnesota, USA
[2]Health Sciences Research, Mayo, Rochester, Minnesota, USA

Correspondence to Dr Elena Myasoedova, Rheumatology, Mayo Clinic, Rochester, MN 55905, USA; myasoedova.elena@mayo.edu

Twitter Elena Myasoedova @MyasoedovaElena and John Davis @JohnDavisIII

Contributors All authors discussed the response and contributed to the final manuscript. EM wrote the manuscript in consultation with JD, ELM and CSC.

Funding This work was funded by a grant from the National Institutes of Health, National Institute of Arthritis and Musculoskeletal and Skin Diseases (R01 AR46849). Research reported in this publication was supported by the National Institute of Aging of the National Institutes of Health under award number R01AG034676.

Disclaimer The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, conduct, reporting or dissemination plans of this research.

Patient consent for publication Not required.

Provenance and peer review Commissioned; internally peer reviewed.

To cite Myasoedova E, Davis J, Matteson EL, *et al*. *Ann Rheum Dis* 2022;**81**:e70.

Received 7 May 2020
Accepted 12 May 2020
Published Online First 29 May 2020

Linked

► http://dx.doi.org/10.1136/annrheumdis-2020-217609

Ann Rheum Dis 2022;**81**:e70. doi:10.1136/annrheumdis-2020-217900

ORCID iDs
Elena Myasoedova http://orcid.org/0000-0003-2006-1436
Cynthia S Crowson http://orcid.org/0000-0001-5847-7475

REFERENCES

1 Myasoedova E, Davis J, Matteson EL, *et al*. Is the epidemiology of rheumatoid arthritis changing? results from a population-based incidence study, 1985-2014. *Ann Rheum Dis* 2020;79:440–4.
2 Matthijssen XME, Huizinga TWJ, van der Helm-van Mil AHM. Increasing incidence of autoantibody-negative RA is replicated and is partly explained by an aging population. *Ann Rheum Dis* 2020;81:e69.
3 Coffey CM, Crowson CS, Myasoedova E, *et al*. Evidence of diagnostic and treatment delay in seronegative rheumatoid arthritis: missing the window of opportunity. *Mayo Clin Proc* 2019;94:2241–8.
4 Trouw LA, Rispens T, Toes REM. Beyond citrullination: other post-translational protein modifications in rheumatoid arthritis. *Nat Rev Rheumatol* 2017;13:331–9.