Increasing incidence of autoantibody-negative RA is replicated and is partly explained by an aging population

With great interest, we read the recently published report by Myasoedova *et al* in which a significant increase in incidence of rheumatoid factor (RF)-negative rheumatoid arthritis (RA) was found, in contrast to RF-positive RA.[1] Studies on trends of RA-incidence stratified for autoantibodies are scarce. Moreover, both an increase and decrease in incidence of RF-negative RA has been reported.[2 3] Because validation is important, we determined trends in incidence of RA over two decades in our region.

We defined autoantibody-positivity as autocitrullinated protein antibodies (ACPA)-positivity, since RF is less specific for RA and more often present in healthy controls, especially at older age.[4] Second, because autoantibody-negative RA has an higher age-of-onset than autoantibody positive RA,[5] we hypothesised that part of the incidence increase is explained by ageing of the population. Therefore, we also assessed the influence of the population age-distribution on the trends of incidence of RA.

Incidence rates were calculated based on the inclusion rate of patients with RA in the Leiden Early Arthritis Cohort (EAC). The Leiden University Medical Center (LUMC) is the only rheumatology referral centre within the Leiden area and inclusion in the EAC of newly presenting patients with early arthritis has been part of regular care since 1993.[6] All consecutively included patients with RA (defined as clinical diagnosis plus fulfilling the 1987 or 2010-criteria within 1 year) included in the EAC between 1994 and 2015 were studied.

First, we calculated crude incidence rates per year using the number of incident cases as the numerator and total population counts from the NUTS-3 (Nomenclature of Territorial Units for Statistics) region around Leiden as the denominator.[7] Trends over time were analysed with Poisson regression. Next, to assess the influence of age-changes in the Leiden population, a three degree of freedom spline of age was included in the Poisson models. All analyses were stratified for ACPA (anti-cyclic citrullinated peptide (CCP)2)-status, which was determined after inclusion but rarely by general practioners in line with Dutch guidelines.[8]

A total of 1697 patients with RA were included between 1994 and 2015 (mean age 57, 66% female, 48% ACPA-positive). For the total RA population, a crude incidence increase was observed (β=0.020 (95% CI 0.012 to 0.027), figure 1). This estimate approximates the proportion increase per year, where 0.02 translates to ~2% increase per year. Stratification for ACPA-status revealed that the crude incidence of ACPA-negative RA increased (0.028 (0.017 to 0.039)) while ACPA-positive RA did not significantly increase (0.009 (–0.002 to 0.021)). We thereby replicated the findings of Myasoedova *et al*. Further stratification for IgM-RF-status within ACPA-negative RA revealed no significant differences in the increase in crude incidence between RF-positive ACPA-negative and RF-negative ACPA-negative RA (0.039 (0.017 to 0.061) vs 0.023 (0.011 to 0.036); p=0.22)).

ACPA-negative RA had the peak incidence at higher age (mean age at diagnosis 59 vs 54; p<0.001; figure 2A), which is in line with previous observations.[5] We then adjusted incidence rates for the changes in age distribution in our healthcare region 1994–2015. This revealed lower estimates in both ACPA-subsets, suggesting that part of the crude incidence increase was due to ageing. After this age-correction, the incidence of ACPA-negative RA still showed some remaining increase over
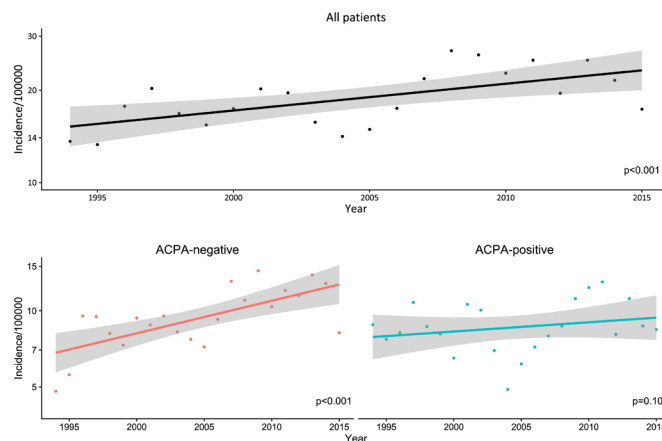

Figure 1 Crude incidence of RA in the Leiden area 1994–2015 in all patients (above) and stratified for ACPA (below): Y-axis is presented on the log-scale. Dots depict the observations per year. Fitted linear lines are depicted in bold and confidence intervals in light grey. ACPA, autocitrullinated protein antibodies; RA, rheumatoid arthritis.

time (0.017 (0.006 to 0.028)). Also here, there was no increased incidence in ACPA-positive RA (0.000 (–0.011 to 0.012)).

Because we observed that the increase in incidence of the past decades was partly explained by ageing of the population, and it is known that the population will age even more, we estimated the further increase in ACPA-negative RA for the coming two decades based on ageing using age-specific Dutch population prognoses of Statistics Netherlands.[9] As presented in figure 2B, the estimated increase of new RA cases the next 20 years due to ageing of the population is 11% in ACPA-negative RA and 2% in ACPA-positive RA.

Our analyses are based on the assumption that all incident RA cases in the region are included in the EAC. This assumption is supported by the fact that the LUMC is the only referral centre in the region. Importantly, the referral region and strategy has not changed during the last two decennia; hence, if a proportion of patients with novel RA is not included in the cohort, this is presumably similar over time and does not affect our results on trends over time.
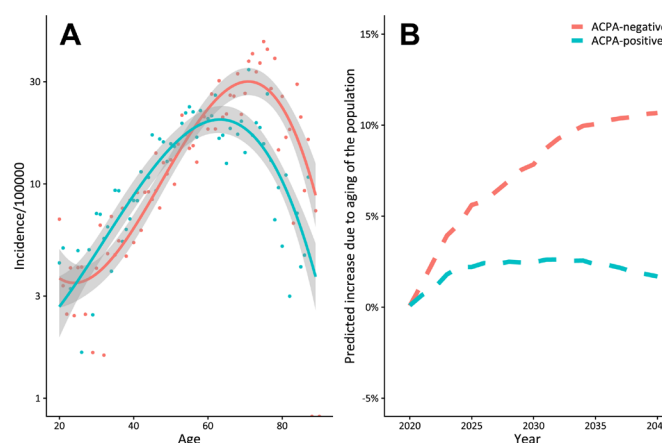
Figure 2 Crude incidence per age (A) and predicted increase in incidence due to ageing of the Dutch population (B), both for ACPA-negative and ACPA-positive RA. (A) Y-axis is presented on the log-scale. Dots depict the observations per age. Fitted lines are depicted in bold and CIs in light grey. ACPA, autocitrullinated protein antibodies; RA, rheumatoid arthritis.

In conclusion, we found an increasing incidence of ACPA-negative RA that was absent in ACPA-positive RA, which is line with the findings of Myasoedova *et al*. Moreover, we showed that the increase in ACPA-negative RA was in part explained by ageing of the population. This will make ACPA-negative RA more prevalent the coming years and promotes the need for research in this subset of RA.

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