EXTENDED REPORT

Presence of anticitrullinated protein antibodies in a large population-based cohort from the Netherlands

A van Zanten, S Arends, C Rouzendaal, P C Limburg, F Maas, L A Trouw, R E M Toes, T W J Huizinga, H Bootsma, E Brouwer

ABSTRACT

Objectives To determine the prevalence of anticitrullinated protein antibodies (ACPAs) and their association with known rheumatoid arthritis (RA) risk factors in the general population.

Methods Lifelines is a multidisciplinary prospective population-based cohort study in the Netherlands. Cross-sectional data from 40 136 participants were used. The detection of ACPA was performed by measuring anti-CCP2 on the Phadia-250 analyser with levels ≥6.2 U/mL considered positive. An extensive questionnaire was taken on demographic and clinical information, including smoking, periodontal health and early symptoms of musculoskeletal disorders. RA was defined by a combination of self-reported RA, medication use for the indication of rheumatism and visiting a medical specialist within the last year.

Results Of the total 40 136 unselected individuals, 401 (1.0%) had ACPA level ≥6.2 U/mL. ACPA positivity was significantly associated with older age, female gender, smoking, joint complaints, RA and first degree relatives with rheumatism. Of the ACPA-negative participants, 22.4% had RA (15.2% had defined RA according to our criteria and 7.2% self-reported RA only). In participants without RA, 311 (0.8%) were ACPA-positive. In the non-RA group, older age, smoking and joint complaints remained significantly more frequently present in ACPA-positive compared with ACPA-negative participants.

Conclusions In this large population-based study, the prevalence of ACPA levels ≥6.2 U/mL was 1.0% for the total group and 0.8% when excluding patients with RA. Older age, smoking and joint complaints were more frequently present in ACPA-positive Lifelines participants. To our knowledge, this study is the largest study to date on ACPA positivity in the general, mostly Caucasian population.

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic autoimmune disease primarily targeting the joints.1 It is thought that early treatment with disease-modifying anti-rheumatic drugs (DMARDs) and possibly steroids can prevent progression of the disease and may even change or prevent the development of erosive disease.2 A systemic review in early RA demonstrated that longer symptom duration is associated with more radiographic progression and lower chance of DMARD-free sustained remission, supporting the idea of a therapeutic ‘window of opportunity’.3 Early detection of RA is therefore crucial.

Previous studies have shown that persons with arthralgia are at risk for developing RA.4 This risk is even higher when the arthralgia is combined with anticitrullinated protein antibody (ACPA) positivity.5 Patients with clinically suspected arthralgia who show subclinical inflammation on MRI were more often ACPA-positive than those without inflammation on MRI, and were at high risk of developing arthritis.6 Individuals with new non-specific musculoskeletal symptoms but without clinical synovitis were at high risk of rapidly progressing to RA when they tested ACPA-positive.7 Therefore, ACPA status can provide important information on both diagnosis and prognosis.4 8–10

Depending on the method of ACPA detection and the cut-off value used, 55–91% of patients with RA are considered ACPA-positive compared with 0–9% of healthy control subjects.11–13 It has been shown that the switch to ACPA positivity can occur up to 10 years before a patient develops arthritis. Early serum samples from patients with classified RA that were blood bank donors were ACPA-positive in 31–41% of cases.11 14 15 Similarly, first-degree relatives (FDRs) are more likely ACPA-positive than normal controls.12–14 17

In a prospective study of 374 individuals who reported arthralgia and had a positive ACPA and/or IgM-rheumatoid factor (RF) status, 35% developed arthritis after a median follow-up of 12 months. Patients who developed arthritis were more often ACPA-positive. However, the presence of antibodies alone had insufficient predictive power and needed to be combined with other clinical parameters.5 The European League Against Rheumatism Standing Committee on Investigative Rheumatology has pointed out that better insights in early symptoms, ACPA testing and risk factors from patient history are necessary for the development of a predictive model for RA in the years to come.18–19

To date, little is known about the presence of ACPA in the general population. One recent population-based study in Japan (n=9575) showed an ACPA positivity prevalence of 1.7%20 and a Turkish study (n=941) showed a prevalence of 1.0%.21 So far, only one other population-wide study has been published on the prevalence of ACPA positivity in Europe. In this Swedish twin study (n=12 590) 2.8% were ACPA-positive, including patients with RA.22 The exact relationship between known RA risk factors, such as age, gender, tobacco, joint complaints and having FDR with RA20 23 24 and the development of ACPA positivity needs to be further investigated.25
The aim of the present study was to determine the prevalence of ACPA positivity on a population level and to determine its association with known RA risk factors. In this respect, we investigated whether previously described risk factors for RA and ACPA development were also more often present in individuals who were ACPA-positive within the Lifelines general population.

MATERIALS AND METHODS
Study design and study population
Lifelines is a multidisciplinary prospective population-based cohort study examining in a unique three-generation design the health and health-related behaviours of 167 729 persons living in the north-east region of the Netherlands. It employs a broad range of investigative procedures in assessing the biomedical, sociodemographic, behavioural, physical and psychological factors which contribute to the health and disease of the general population, with a special focus on multimorbidity and complex genetics. Lifelines is a facility that is open for all researchers. Information on application and data access procedure is summarised on http://www.Lifelines.net.

Participants were recruited with the help of general practitioners from both rural and non-rural areas and from different economic classes. Participants were then asked to invite their family members, making it into a three-generation population-based cohort.26 This cohort well represents the northern, mostly Caucasian, population of the Netherlands.27

Data for the present study were acquired at baseline visits (2012–2013). Participants under 18 years of age were excluded. An extensive questionnaire was handed in, physical examination was performed and serum blood samples were collected. The family history was obtained at the first follow-up visit 1.5 years later.26

The Lifelines Cohort Study was conducted according to the principles of the Declaration of Helsinki, approved by the local ethics committee of the University Medical Center Groningen (UMCG), and all participants provided written informed consent to participate in this study.

ACPA measurement
The detection of ACPA was performed by measuring anti-CCP2 (by EliA-cyclic citrullinated peptide (CCP) test) on the Phadia-250 analyser. The measuring range (detection limit, upper limit) for EliA CCP is from 0.4 EliA U/mL to >340 EliA U/mL.

ACPA-CCP2 levels ≥6.2 U/mL were considered positive, based on data of 400 apparently healthy controls obtained from ThermoFisher Scientific. The cut-off value that is appropriate to detect ACPA in the healthy population is not clear. As we wanted to use the test to detect ACPA and not as a diagnostic test for RA, the 99-centile cut-off value of ≥6.2 U/mL was used. Analyses were also done using the 95-centile cut-off value of ≥4.3 U/mL and the manufacturer’s cut-off value for RA of ≥10 U/mL.

Assessment of risk factors
Risk factors for RA and ACPA were determined using literature analysis on PubMed. Access to data on these risk factors was then assessed. Risk factors that could be included in the analyses were age, gender, body mass index (BMI), use of tobacco, alcohol, fish and/or sugar-sweetened soft drinks, periodontitis, joint complaints and FDRs with rheumatism. For women nulliparity, menopausal status and hormone use, regular menses and early menarche were assessed. Definitions of these risk factors are shown in online supplementary table S1.

Definition of RA
Patients with RA were identified using data from the questionnaire. A participant was classified as a self-reported patient with RA if the question on having RA was answered positive. A participant was classified as patient with defined RA if there was either a combination of self-reported RA and the use of a DMARD for the indication of ‘rheumatism’ or a combination of self-reported RA, the use of steroids and/or non-steroidal anti-inflammatory drugs (NSAIDs) for the indication of ‘rheumatism’ and having been to a medical specialist within the last year. An overview of included DMARDs and NSAIDs is given in online supplementary table S2.

Statistical analysis
Results were expressed as percentage of participants, mean±SD or median (IQR) for categorical, normally distributed and non-normally distributed data, respectively.

To assess whether the risk factors found in literature were correlated with ACPA positivity, participants were stratified according to ACPA positivity. We performed the same analyses excluding all patients with RA and defined patients with RA from the total populations. For all three analyses, χ² tests, Mann-Whitney U tests and univariable logistic regression were performed to assess the differences.

Multivariable logistic regression (enter method, forward selection and backward elimination) was performed to assess which factors were independent predictors of ACPA positivity. Parameters were added into the model if they were found to be significantly associated with ACPA positivity in the previous analyses. If there was more than one variable for the same factor, the strongest predictor of ACPA positivity was used. Multivariable analysis was performed both for the entire group and excluding defined or self-reported patients with RA.

Statistical analysis was performed with IBM SPSS Statistics V22 (SPSS, Chicago, Illinois, USA). p Values ≤0.05 were considered statistically significant.

RESULTS
Study population
In total, 40 136 participants were recruited for this study, of whom 23 256 (58%) were female. The mean age was 44 (range 18–92). Among these participants, 838 (2.1%) had self-reported RA and 138 (0.3%) were defined as having RA (table 1, online supplementary table S3).

Distribution of ACPA-CCP2 levels
Of all participants, 401 (1.0%) had an ACPA-CCP2 level ≥6.2 U/mL, 666 (1.7%) had an ACPA-CCP2 level ≥4.3 and 306 (0.8%) had an ACPA-CCP2 level ≥10 U/mL. The detailed distribution of ACPA levels among participants is presented in table 2.

ACPA positivity (≥6.2 U/mL) was seen in 90 (10.7%) of patients with self-reported RA and 61 (44.2%) of patients with defined RA. In participants without RA (non-RA group), 311 (0.8%) were ACPA-positive. The prevalence of both ACPA positivity and RA increased with age (table 3).

ACPA-positive versus ACPA-negative participants
ACPA-positive (≥6.2 U/mL) participants were significantly older and more often female compared with the ACPA-negative participants. Furthermore, ACPA-positive participants had more pack years of smoking and had less often never smoked. Joint complaints and FDRs with rheumatism were also significantly more often reported. Moreover, ACPA-positive participants had
Clinical and epidemiological research

Table 1  Baseline characteristics: all participants

| Characteristic                        | All (n=40 136) |
|---------------------------------------|---------------|
| Age (years)                           | 44 (34–51)    |
| Gender (female)                       | 58%           |
| BMI (kg/m²)                           | 25 (23–28)    |
| Obesity                               | 15%           |
| Smoking (pack years)                  | 0 (0–8)       |
| Smoking status                        |               |
| Never smoker                          | 49%           |
| Former smoker                         | 30%           |
| Current smoker                        | 21%           |
| Alcohol intake (g/day)                | 3 (0–11)      |
| Fish intake (servings/month)          | 5 (2–9)       |
| Sugar-sweetened soft drink intake (glasses/month) | 6 (0–22) |
| Periodontitis (self-reported)         | 12%           |
| Joint complaints: pain and/or stiffness in hands and/or feet | 21% |
| Joint complaints: both pain and stiffness in hands and/or feet | 12% |
| FDR with rheumatism                   | 14%           |
| Self-reported RA                      | 2.1%          |
| Defined RA                            | 0.3%          |
| In women (n=23 256)                   |               |
| Nulliparity                           | 27%           |

Table 2  Distribution of anticitrullinated protein antibody levels among participants

| Antibody Level | All (n=40 136; %) | No RA (n=39 298; %) | Self-reported RA (n=838; %) | Defined RA (n=138; %) |
|----------------|-------------------|---------------------|-----------------------------|-----------------------|
| ≥6.2 U/mL      | 1.0               | 0.8                 | 10.7                        | 44.2                  |
| <4.3 U/mL      | 98.3              | 98.5                | 88.5                        | 55.1                  |
| 4.3–6.2 U/mL   | 0.7               | 0.7                 | 0.8                         | 0.7                   |
| 6.2–10 U/mL    | 0.2               | 0.2                 | 0.4                         | 0.7                   |
| ≥10 U/mL       | 0.8               | 0.6                 | 10.3                        | 43.5                  |

RA, rheumatoid arthritis.

Table 3  The distribution of the Lifelines population, anticitrullinated protein antibodies (ACPA) positivity, self-reported rheumatoid arthritis (RA) and defined RA among different age groups

| Age (years) | Lifelines population (%) | ACPA positivity (≥6.2 U/mL; %) | Self-reported RA (%) | Defined RA (%) |
|-------------|--------------------------|---------------------------------|----------------------|----------------|
| 18–30       | 16.5                     | 0.6                             | 0.5                  | 0.1            |
| 30–40       | 19.7                     | 0.8                             | 1.0                  | 0.1            |
| 40–50       | 34.4                     | 0.9                             | 2.0                  | 0.3            |
| 50–60       | 19.7                     | 1.4                             | 3.3                  | 0.7            |
| 60+         | 9.7                      | 1.5                             | 5.0                  | 0.8            |

RA, rheumatoid arthritis.

substantially more frequently self-reported or defined RA (table 4). When using a cut-off value of ≥4.3 U/mL or ≥10 U/mL, similar results were found. Additionally for ≥10 U/mL, ACPA-positive participants reported significantly less use of sugar-sweetened soft drinks and women were less often nulliparous (data not shown).

In the population without RA or self-reported RA, older age, smoking and joint complaints remained associated with ACPA positivity (≥6.2 U/mL) (table 5). In this group, gender, BMI, alcohol intake, fish intake, sugar-sweetened soft drink intake, periodontitis and FDR with rheumatism were comparable between ACPA-positive and ACPA-negative participants. Within the female study population, nulliparity, menopausal status and hormone use, early menarche and regular menses were not associated with ACPA positivity. When a cut-off value of ≥4.3 U/mL or ≥10 U/mL was used, similar results were found.

Independent predictors of ACPA positivity

Using multivariable analysis, pack years of smoking was the strongest smoking variable predicting ACPA positivity and not smoking status (never, former or current). Gender, pack years of smoking and joint complaints were independent predictors of ACPA positivity (table 6). When excluding self-reported and/or defined RA participants, only gender and pack years remained statistically significant.

DISCUSSION

In this large cross-sectional population-based study (n=40 136), the prevalence of ACPA positivity was 1.0% on a population level and 0.8% when excluding RA participants, using ACPA-CCP2 ≥6.2 U/mL (99th centile) as the cut-off point.

Three previous studies investigated the prevalence of ACPA positivity in the general population. In a Japanese study,20 (n=9575), the reported prevalence was 1.7% in autoimmune disease-free volunteers aged 30–75 years using a Japanese CCP2-Kit. A Turkish study21 (n=941) found a prevalence of 1.0% in a healthy population using a Eurodiagnostica second-generation anti-CCP antibody assay. A twin study in Sweden found an (n=12 590) ACPA positivity (including patients with RA) of 2.8% using an anti-CCP2 ELISA Eurodiagnostica assay.22 However, as the first two studies were performed in non-Caucasian populations and all studies used different ACPA-CCP assays with different cut-off levels, it is difficult to compare their results with our study.

In our study population, ACPA positivity was significantly associated with several risk factors for RA and/or ACPA as found in literature.

First, we found an association between older age and ACPA positivity, both in the entire group and in the non-RA group. In agreement with our study, the Japanese study found that in non-RA individuals ACPA positivity was associated with older age.20

Second, we found an association between female gender and ACPA positivity, which has not yet been well documented, although RA is more prevalent among women.23 In our study, female gender remained significantly associated with ACPA positivity after correcting for age, smoking and joint complaints. However, when excluding patients with RA, female gender was no longer associated with ACPA positivity.

Third, we found an association of both smoking status and pack years with ACPA positivity, which was reported in previous studies as well. A Malaysian case-control study (n=1056 vs 1416) found that ever-smokers had an increased risk of developing ACPA-positive RA compared with never smokers. A relation
between pack years and the risk of ACPA-positive RA was also seen, with an OR of 3.3 for <20 pack years and an OR of 5.2 for at least 20 pack years. This is in contrast to the Japanese population-based study, where only a significant association between the amount of smoking and high levels of ACPA was found.29 This is in contrast to the Japanese population-based study, where only a significant association between the amount of smoking and high levels of ACPA was found.29 This is in contrast to the Japanese population-based study, where only a significant association between the amount of smoking and high levels of ACPA was found.29 This is in contrast to the Japanese population-based study, where only a significant association between the amount of smoking and high levels of ACPA was found.29

Finally, joint complaints were found to be an independent risk factor for ACPA positivity, even with the limited joint complaint questions that were asked to the participants. Also, in non-RA participants the presence of joint complaints stayed significantly different between ACPA-positive and ACPA-negative participants after correcting for age, gender and smoking.

FDRs of patients with RA were found to be more often ACPA-positive.14 In our study population, having FDRs with rheumatism not being associated with RA. The ACPA cut-off value was difficult to determine since all tests and their specificities and sensitivities are based on using the test as a diagnostic tool for RA. However, after consulting the manufacturer and taking into account data on November 8, 2022 by guest. Protected by copyright.
controls, we decided that 6.2 U/mL (99th centile) is an appropriate cut-off value. This cut-off value was lower than the cut-off value used in the diagnostic test for RA (≥10 U/mL) in order to get an insight into the presence of ACPA.

Second, many people regard themselves as having RA when they experience joint complaints, but they have not always been diagnosed by a doctor. Therefore, we checked RA-specific medication use and visits to a medical specialist in these patients with self-reported RA. As this database was large, the indexing that was used to find the medication of interest may have missed some patients with RA. To make the selection of patients with defined RA more secure, the indications of the drugs were checked by hand. Since ACPA positivity shows a steep curve from non-RA to self-reported RA to defined RA, we concluded that our definition is a good estimate for RA. However, the prevalence we found for defined RA is somewhat low, which makes it likely that some patients were missed using this definition. Additionally, the prevalence of ACPA positivity was only 44% in our defined RA population, whereas previous literature has shown that 55–91% of patients with RA are considered ACPA-positive. This means that our defined RA group likely also contains some individuals without RA. It is important to realise that our definition was not RA classified by a rheumatologist and misclassification could have occurred.

Another limitation of this study is that even though we did find significant differences between the different groups, the ORs were only small. The clinical use of those small differences should be interpreted with caution. Moreover, the present analysis was cross-sectional and therefore, the causality of our findings cannot be claimed. Unfortunately, we did not yet have access to genetic information about our participants, even though this is seen as an important factor for determining the switch to RA. Furthermore, our data on joint complaints was limited. It would have been helpful if more specific RA symptoms were assessed at baseline. Also data on breast feeding, birth weight and other relevant autoantibodies like RF and anti-carbamylated protein (CarP) antibodies were not available.

To our knowledge, this is the first study that measured ACPA in >40 000 participants from a general, mostly Caucasian population. As the Lifelines study is a prospective longitudinal cohort study with 30-year follow-up duration, it will be possible to gain follow-up information on our study population. It will be interesting to see which participants will eventually develop RA. Will the participants who reported having RA but did not yet have defined RA develop defined RA? These future results from the Lifelines cohort study will help us in improving the existing...
Table 6  Univariable and multivariable logistic regression for RA risk factors and ACPA positivity (≥6.2 U/mL) in all participants and after exclusion of RA participants

|                                      | Univariable | Multivariable |
|--------------------------------------|-------------|---------------|
|                                      | OR | 95% CI | p Value | OR | 95% CI | p Value |
| All participants (n=40 136)          |    |        |         |    |        |         |
| Age (years)                          | 1.023 | 1.014 to 1.031 | <0.001 | 1.013 | 1.003 to 1.022 | 0.007 |
| Gender (female)                      | 1.342 | 1.092 to 1.649 | 0.005 | 1.325 | 1.069 to 1.643 | 0.010 |
| Smoking: pack years                  | 1.023 | 1.015 to 1.030 | <0.001 | 1.018 | 1.009 to 1.026 | <0.001 |
| Pack years, categories (%)           |    |        |         |    |        |         |
| Never to 10                          |    |        |         |    |        |         |
| >10–20                               | 1.136 | 0.835 to 1.546 | 0.416 |     |        |         |
| >20                                  | 2.311 | 1.763 to 3.030 | <0.001 |     |        |         |
| Smoking status                       |    |        |         |    |        |         |
| Never smoker                         |    |        |         |    |        |         |
| Current smoker                       | 1.532 | 1.221 to 1.923 | 0.000 |     |        |         |
| Current smoker                       | 1.499 | 1.164 to 1.929 | 0.002 |     |        |         |
| Alcohol intake (g/day)               | 1.001 | 0.991 to 1.011 | 0.852 |     |        |         |
| Joint complaints: pain and/or stiffness in hands and/or feet | 2.384 | 1.945 to 2.923 | <0.001 |     |        |         |
| Joint complaints: both pain and stiffness in hands and/or feet | 2.976 | 2.390 to 3.705 | <0.001 |     | 2.556 | 2.033 to 3.215 | <0.001 |
| Self-reported RA                     | 15.083 | 11.800 to 19.281 | <0.001 |     |        |         |
| Defined RA                           | 92.404 | 64.953 to 131.456 | <0.001 |     |        |         |
| Participants with RA excluded (n=39 298) |    |        |         |    |        |         |
| Age (years)                          | 1.010 | 1.001 to 1.020 | 0.032 |     | 1.003 | 0.993 to 1.014 | 0.517 |
| Gender (female)                      | 1.211 | 0.962 to 1.524 | 0.104 |     | 1.289 | 1.014 to 1.639 | 0.038 |
| Smoking: pack years                  | 1.019 | 1.010 to 1.028 | <0.001 |     | 1.019 | 1.009 to 1.028 | <0.001 |
| Pack years, categories (%)           |    |        |         |    |        |         |
| Never to 10                          |    |        |         |    |        |         |
| >10–20                               | 1.070 | 0.752 to 1.524 | 0.706 |     |        |         |
| >20                                  | 1.915 | 1.379 to 2.659 | <0.001 |     |        |         |
| Smoking status                       |    |        |         |    |        |         |
| Never smoker                         |    |        |         |    |        |         |
| Former smoker                        | 1.438 | 1.111 to 1.863 | 0.006 |     |        |         |
| Current smoker                       | 1.465 | 1.102 to 1.946 | 0.008 |     |        |         |
| Alcohol intake (g/day)               | 0.995 | 0.983 to 1.008 | 0.463 |     |        |         |
| Joint complaints: pain and/or stiffness in hands and/or feet | 1.364 | 1.055 to 1.764 | 0.018 |     |        |         |
| Joint complaints: both pain and stiffness in hands and/or feet | 1.422 | 1.040 to 1.943 | 0.027 |     | 1.275 | 0.923 to 1.762 | 0.140 |

Data are presented as ORs and CIs of the enter method. Forward and backward analyses resulted in comparable models with the same variables.

ACPA, anticitrullinated protein antibodies; RA, rheumatoid arthritis.

In conclusion, this large, cross-sectional, population-based study in 40 136 mostly Caucasian Lifelines participants showed that the prevalence of ACPA-CCP2 positivity is 1.0% for the total population and 0.8% when excluding patients with RA (ACP...
Clinical and epidemiological research

permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/

REFERENCES

1. Firestein GS. Evolving concepts of rheumatoid arthritis. Nature 2003;423:356–61.
2. Heidari B. Rheumatoid Arthritis: eEarly diagnosis and treatment outcomes. Caspian J Intern Med 2011;2:161–70.
3. van Nies JA, Krabben A, Schoones JW, et al. What is the evidence for the presence of a therapeutic window of opportunity in rheumatoid arthritis? A systematic literature review. Ann Rheum Dis 2014;73:861–70.
4. van de Stadt LA, Witte BI, Bos WH, et al. A prediction rule for the development of arthritis in seropositive arthralgia patients. Ann Rheum Dis 2013;72:1920–6.
5. Bos WH, Wobink GJ, Boers M, et al. Arthritis development in patients with arthralgia is strongly associated with anti-citrullinated protein antibody status: a prospective cohort study. Ann Rheum Dis 2010;69:490–4.
6. van Steenbergen HW, van Nies JA, Huizinga TW, et al. Characterising arthralgia in the preclinical phase of rheumatoid arthritis using MRI. Ann Rheum Dis 2015;74:1225–32.
7. Nam JI, Hunt L, Hensor EM, et al. Enriching case selection for imminent RA: the use of anti-CCP antibodies in individuals with new non-specific musculoskeletal symptoms—a cohort study. Ann Rheum Dis 2016;75:1452–6.
8. Seegobin SD, Ma MH, Dahanuque C, et al. ACJ-positive and ACJ-negative rheumatoid arthritis differ in their requirements for combination DMARDs and corticosteroids: secondary analysis of a randomized controlled trial. Arthritis Res Ther 2014;16:R13.
9. De Rooy DP, Willemsen A, Mertens B, et al. Can anti-citrullinated peptide antibody-negative RA be subdivided into clinical subphenotypes? Arthritis Res Ther 2011;13:R180.
10. van der Helm-van Mil AH, Verpoort KN, Breedveld FC, et al. Antibodies to citrullinated proteins and differences in clinical progression of rheumatoid arthritis. Arthritis Res Ther 2005;7:R949–58.
11. Jørgensen KT, Wiik A, Pedersen M, et al. Antibodies recognizing carbamylated peptides and rheumatoid factor in rheumatoid arthritis patients and relatives from Brazil. Rheumatology (Oxford) 2016;73:861–9.
12. de Pablo P, Dietrich T, Chapple IL, et al. The autoantibody repertoire in periodontitis: a role in the induction of autoimmunity to citrullinated proteins in rheumatoid arthritis? Ann Rheum Dis 2014;73:580–6.
13. Scott IC, Tan R, Stahl D, et al. The protective effect of alcohol on developing rheumatoid arthritis: a systematic review and meta-analysis. Rheumatology (Oxford) 2013;52:856–67.
14. Costenbader KH, Feskanich D, Mandl LA, et al. Smoking intensity, duration, and cessation, and the risk of rheumatoid arthritis in women. Am J Med 2006;119:503–e1–9.
15. Rosell M, Wesley AM, Rydén K, et al. Dietary fish and fish oil and the risk of rheumatoid arthritis. Epidemiology 2009;20:896–901.
16. Hu Y, Costenbader KH, Gao X, et al. Sugar-sweetened soda consumption and risk of developing rheumatoid arthritis in women. Am J Clin Nutr 2014;100:959–67.
17. Neovius M, Simard JF, Askling J, et al. Nationwide prevalence of rheumatoid arthritis and penetration of disease-modifying drugs in Sweden. Ann Rheum Dis 2011;70:624–9.
18. Jutley G, Raza K, Buckley CD. New pathogenic insights into rheumatoid arthritis. Curr Opn Rheumatol 2015;27:240–5.
19. Chan H, Wang J, Zhou W, et al. Breastfeeding and risk of rheumatoid arthritis: a systematic review and meta-analysis. J Rheumatol 2015;42:1563–9.
20. Mandl LA, Costenbader KH, Simard JF, et al. Is birthweight associated with risk of rheumatoid arthritis? Data from a large cohort study. Ann Rheum Dis 2009;68:514–18.
21. Tasiilyurt T, Kisacik B, Kaya SU, et al. The frequency of antibodies against cyclic citrullinated peptides and rheumatoid factor in healthy population: a field study of rheumatoid arthritis from northern Turkey. Rheumatol Int 2013;33:939–42.
22. Hervold AH, Frisell T, Magnusson PK, et al. How well do ACJ discriminate and predict RA in the general population: a study based on 12 590 population-representative Swedish twins. Ann Rheum Dis 2016; Published Online First 28 April 2016.
23. Källberg H, Ding B, Padyukov L, et al. Smoking is a major preventable risk factor for rheumatoid arthritis: estimations of risks after various exposures to cigarette smoke. Ann Rheum Dis 2011;70:508–11.
24. Sparks JA, Chang SC, Deane KD, et al. Associations of smoking and age with inflammatory joint signs among unaffected first-degree relatives of rheumatoid arthritis patients: results from studies of the etiology of rheumatoid arthritis. Ann Rheum Dis 2016;68:1828–38.
25. Gerlag DM, Norris JM, Tak PP. Towards prevention of autoantibody-positive rheumatoid arthritis: from lifestyle modification to preventive treatment. Rheumatology (Oxford) 2016;55:607–14.
26. Scholten S, Smith N, Swertz MA, et al. Cohort Profile: lifelines, a three-generation cohort study and biobank. Int J Epidemiol 2015;44:1172–80.
27. Klis B, Scholten S, Mandemakers JI, et al. Representativeness of the lifelines cohort study. PLoS ONE 2015;10:e0131703.
28. Brennan P, Silman A. Why the gender difference in susceptibility to rheumatoid arthritis? Arthritis Rheum 1995;34:694–5.
29. Yahya A, Bengtsson C, Lai TC, et al. Smoking is associated with an increased risk of developing ACPA-positive but not ACPA-negative rheumatoid arthritis in Asian populations: evidence from the Malaysian MyEIRA case-control study. Mod Rheumatol 2012;22:524–31.
30. Sparks JA, Chen CY, Hikini LT, et al. Contributions of familial rheumatoid arthritis or lupus and environmental factors to risk of rheumatoid arthritis in women: a prospective cohort study. Arthritis Care Res (Hoboken) 2016;64:1438–46.
31. de Pablo P, Dietrich T, Chapple IL, et al. The autoantibody repertoire in periodontitis: a role in the induction of autoimmunity to citrullinated proteins in rheumatoid arthritis? Ann Rheum Dis 2014;73:580–6.
32. Scott IC, Tan R, Stahl D, et al. The protective effect of alcohol on developing rheumatoid arthritis: a systematic review and meta-analysis. Rheumatology (Oxford) 2013;52:856–67.
33. Costenbader KH, Feskanich D, Mandle LA, et al. Smoking intensity, duration, and cessation, and the risk of rheumatoid arthritis in women. Am J Med 2006;119:503–e1–9.
34. Rosell M, Wesley AM, Ryden K, et al. Dietary fish and fish oil and the risk of rheumatoid arthritis. Epidemiology 2009;20:896–901.
35. Hu Y, Costenbader KH, Gao X, et al. Sugar-sweetened soda consumption and risk of developing rheumatoid arthritis in women. Am J Clin Nutr 2014;100:959–67.
36. Neovius M, Simard JF, Askling J, et al. Nationwide prevalence of rheumatoid arthritis and penetration of disease-modifying drugs in Sweden. Ann Rheum Dis 2011;70:624–9.
37. Jutley G, Raza K, Buckley CD. New pathogenic insights into rheumatoid arthritis. Curr Opn Rheumatol 2015;27:240–5.
38. Chen H, Wang J, Zhou W, et al. Breastfeeding and risk of rheumatoid arthritis: a systematic review and meta-analysis. J Rheumatol 2015;42:1563–9.
39. Mandl LA, Costenbader KH, Simard JF, et al. Is birthweight associated with risk of rheumatoid arthritis? Data from a large cohort study. Ann Rheum Dis 2009;68:514–18.
40. Kelly CA, Saravanan V, Nisar M, et al. Rheumatoid arthritis-related interstitial lung disease: associations, prognostic factors and physiological and radiological characteristics—a large multicentre UK study. Rheumatology (Oxford) 2014;53:1676–82.
41. Nielsen MM, van Schaardenburg D, Reesink HW, et al. Increased levels of C-reactive protein in serum from blood donors before the onset of rheumatoid arthritis. Arthritis Rheum 2004;50:2423–7.
42. Shi J, Knevel R, Suppannalai P, et al. Autoantibodies recognizing carbamylated proteins are present in sera of patients with rheumatoid arthritis and predict joint damage. Proc Natl Acad Sci USA 2011;108:17372–7.

van Zanten A et al. Ann Rheum Dis 2017;76:1184–1190. doi:10.1136/annrheumdis-2016-209991

Ann Rheum Dis: first published as 10.1136/annrheumdis-2016-209991 on 2 January 2017. Downloaded from http://ard.bmj.com/ on November 8, 2022 by guest. Protected by copyright.