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Presence of Autoantibodies in Males and Females With Rheumatoid Arthritis: A Systematic Review and Metaanalysis

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ABSTRACT. ***Objective.*** Rheumatoid arthritis (RA) is more common in females, and although the cause of RA is unknown, it is characterized by the production of autoantibodies. The aims of this study were to determine whether RA-associated autoantibodies are more often found in females than males and to identify factors that influence the relationship between sex and seropositivity.

Methods. Databases were searched and studies of RA (N ≥ 100) were included if they reported proportion of seropositive patients with RA by sex. Metaanalyses and metaregression were conducted using the random-effects model. Covariates regressed were smoking, age, BMI, Health Assessment Questionnaire–Disability Index (HAQ-DI), and the Disease Activity Score in 28 joints (DAS28).

Results. Eighty-four studies with a total of 141,381 subjects with rheumatoid factor (RF) seropositivity and 95,749 subjects with anticitrullinated protein antibody (ACPA) seropositivity met inclusion criteria. The mean age of participants ranged from 37 to 68 years and the proportion of female subjects ranged from 9% to 92%. Results indicated that females were less likely than males to be seropositive: odds ratio (OR) 0.84 [95% CI 0.77–0.91] for RF and OR 0.88 [95% CI 0.81–0.95] for ACPA. BMI, smoking, mean age, DAS28, and HAQ-DI did not affect the relationship between sex and seropositivity.

Conclusion. Although studies report that females have higher RA disease activity than males and that seropositivity predicts worse outcomes, females were less likely to be seropositive than males.

Key Indexing Terms: autoimmunity, rheumatoid arthritis, seropositivity, sex differences

Rheumatoid arthritis (RA) is the most common autoimmune arthritis with a prevalence of approximately 1%. RA affects females at a rate 2- to 3-times higher than males, although the reasons for this sex discrepancy are not completely understood.[1] The cause of RA is unknown, but it is characterized by autoantibodies—in particular, rheumatoid factor (RF) and anticitrullinated protein antibodies (ACPA). Most studies report that approximately 75% of patients with RA are seropositive.[2] Being seropositive is associated with erosive joint disease, which confers poorer prognosis.[3] Known risk factors for seropositive RA include smoking and the presence of genetic predispositions, such as HLA-DRB1 alleles.[4] Whether the risk of seropositivity differs between males and females is unclear.

Understanding the underlying causes of sex differences in RA is critical, as females are not only more likely to develop RA but also have worse prognosis.[5] Seropositive RA manifests more aggressively than seronegative cases[6,7,8,9,10]; thus, poor prognosis in females could be attributed to a higher frequency of seropositivity than males.

The general aims of this systematic review and metaanalysis were (1) to determine if females with RA are more likely than males to test seropositive for RF and ACPA, and (2) to determine if there are any other demographic, behavioral, or clinical characteristics that may affect the relationship between sex and seropositivity.

METHODS

This systematic review and metaanalysis was registered with PROSPERO (ID: CRD42020156829).[11]

Literature search and study selection. Literature from MEDLINE, Web of Science, Scopus, and EMBASE was searched up to November 10, 2021. The search strategy used for MEDLINE can be found in Supplementary Table 1 (available with the online version of this article). Similar search strategies were used for remaining databases. Duplicates were removed using Mendeley v.1.19.4. Level 1 screening involved title and abstract scanning for predetermined inclusion criteria. Full-text screening was then conducted to determine whether the study reported proportion of females and males seropositive for RF or ACPA. Both level 1 and 2 screening were conducted by 2 reviewers (BH and RY); 84% of studies passing level 2 were agreed upon. Any disagreements were resolved by a third reviewer (LB).

Publications were considered eligible if they (1) investigated RA, (2) were written in English, (3) were an article or abstract, (4) used a sample size of ≥ 100 subjects, and (5) reported RF and/or ACPA by sex. If studies reported data on the same cohort, the largest sample size or most recent publication was included. If data on > 1 eligible cohort were reported separately

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within the same study, these cohorts were entered separately in the meta-analyses and considered as 2 separate studies.

Quality assessment. Quality assessment for observational studies was completed using the Newcastle-Ottawa Scale (NOS).[12] Ranking studies as good, fair, or poor quality was done according to the same methods as Sharmin et al.[13] Cochrane risk of bias tool was used for randomized trials.[14]

Data extraction. Data were extracted from studies using a standardized data collection form. This form included author, year of publication, cohort studied, study design, sample size, total females, total males, separate proportions of females and males seropositive for RF and ACPA, proportion of ever-smokers, and the mean value for age, BMI, Health Assessment Questionnaire–Disability Index (HAQ-DI), and Disease Activity Score in 28 joints (DAS28). If studies reported median values, the median values were assumed to be equal to the mean values. Studies did not distinguish between sex and gender; to be consistent, we report findings as sex. DAS28 measured using erythrocyte sedimentation rate (ESR) was collected unless unavailable, in which case DAS28 using C-reactive protein (CRP) was used. If a study did not specify whether the DAS28 included ESR or CRP, it was assumed to be ESR as this was the most common format employed by the studies.

Statistical analysis. Metaanalyses were carried out using Stata v16.1 (StataCorp) using the random-effects model. For each study, the odds ratios (ORs) for being RF or ACPA positive in females vs males were calculated as described in Supplementary Table 2 (available with the online version of this article).[15] If a study reported zero observations of seropositivity or seronegativity by sex, the continuity correction method was used, with a correction factor of 0.5.[16]

Results are portrayed by forest plots. For each analysis, heterogeneity (reported by the I^2 statistic) was considered for interpretation. Funnel plots were generated to explore the potential for publication bias in both metaanalyses.

Two sensitivity analyses decided a priori were carried out: (1) excluding poor-quality studies and (2) excluding studies published before 2011. To further account for heterogeneity, additional sensitivity analyses were conducted: studies were excluded if the proportion of females and/or the proportion of seropositive individuals fell below the 10th percentile or above the 90th percentile for the total population included in the primary meta-analyses. A subgroup analysis for different ethnic/racial groups was also performed (White, Asian, and Hispanic were the groups reported in the included studies). Finally, a subgroup analysis was conducted according to institutional- vs population-based cohorts.

To explore the effect of potential confounders, random-effects metaregression was carried out with the following variables selected a priori: proportion of ever-smokers, mean age, mean BMI, mean HAQ-DI, and mean DAS28. In Stata, metaregression is conducted by incorporating the effect of covariates (x_j) and an error term for residual heterogeneity that is not accounted for by the covariate (u_j) in the formula: $\theta = \hat{\theta} = x_j B + u_j + \varepsilon_j$.[17]

RESULTS

The databases searched identified 3953 publications: 1615 publications from MEDLINE, 1859 from Scopus, 461 from EMBASE and 18 from Web of Science. Removing duplicates resulted in a total of 3050 publications. Eight hundred twenty-five articles passed level 1 screening. Subsequently, level 2 screening was carried out, consisting of full-article screening, and this resulted in 84 publications that included 87 cohorts to be reviewed and metaanalyzed[6,18–100] (Supplementary Figure 1, available with the online version of this article).

Most of the included studies were published in the year 2000 or later. The mean age ranged from 37 to 68 years and the proportion of females ranged from 9% to 92%. Mean DAS28 ranged from 2.59 to 6.42, therefore ranging from remission to high disease activity (Table 1).

Fifty-five studies, including 58 cohorts, reported RF seropositivity by sex. Data were available for a total of 141,381 patients with RA (103,417 females and 37,964 males). The proportion of males and females seropositive for RF ranged from 4 to 97% and 11 to 97%, respectively.[18,19,21,22,24,25,27,28,30,31,33–36,38,39,43,44,46,47,49–54,56,58–60,62–65,67,70,71,73–75,78,79,81,84,86-93,95,98,99] Fifty-six studies, including 59 cohorts, reported ACPA seropositivity by sex. Data were available for a total of 95,749 patients with RA (70,991 females and 24,758 males). The proportion of males and females seropositive for ACPA ranged from 3 to 100% and 7 to 87%, respectively.[6,19–21,23,24,26,27,29,30,32,36,37,40–49,52,54,55,57,59–62,66,68,69,71,72,74–78,80–83,85,86,89,93–100] Other baseline characteristics for the included studies are summarized in Table 1, and the individual study characteristics can be found in Supplementary Table 3 (available with the online version of this article). It should be noted that the study by Sokolove and colleagues used a sample from Veterans Affairs Database and therefore comprised mostly males, which is not a typical RA demographic.[89]

The NOS tool was used to assess risk of bias for observational studies. Sixty-three studies (64 cohorts) were ranked good quality.[6,19–28,30–36,39–53,55,57–60,62–66,68–73,75,76,79,81,84,89,91–93,95–99] Four were ranked fair quality[38,54,83,87] and 16 (17 cohorts) were ranked poor quality,[18,29,37,56,67,74,77,78,80,82,85,86,88,90,94,100] most commonly due to lack of controlling for relevant confounders. There was 1 randomized clinical trial that was ranked as "some concerns" as blinding was unclear.[61]

Funnel plots were generated to represent the potential for publication bias in both RF and ACPA metaanalyses. Both

Table 1. Summary of the baseline characteristics of the included studies (N = 84 studies, 87 cohorts)

	Range	Studies, n (%)
Study design		
Longitudinal		35 (40)
Cross-sectional		58 (67)
RCT		1 (1)
Sample size, N	100–14,878	87 (100)
Sex		
Female sex, %	9–92	87 (100)
RF+, females vs males, OR	0.18–3.02	58 (66)
ACPA+, females vs males, OR	0.04–3.01	59 (68)
Mean age, yrs	37–68	78 (90)
Ever-smoker, %	8–73	33 (39)
Mean BMI, kg/m^2	22.70–27.80	12 (14)
Mean DAS28	2.59–6.42	39 (44)
Mean HAQ-DI	0.40–1.63	30 (34)
Quality assessment		
Poor		17 (20)
Fair		4 (5)
Good		64 (74)
Some concerns		1 (1)

ACPA: anticitrullinated protein antibody; DAS28: Disease Activity Score in 28 joints; HAQ-DI: Health Assessment Questionnaire–Disability Index; OR: odds ratio; RF: rheumatoid factor.

plots were symmetric, indicating low risk of publication bias (Supplementary Figure 2, available with the online version of this article).

The metaanalysis for RF seropositivity resulted in an overall OR 0.84 (95% CI 0.77–0.91; Figure 1), indicating that the odds of females being RF positive were 16% lower than the odds of males being RF positive. Similarly, the metaanalysis for ACPA seropositivity resulted in an overall OR 0.88 (95% CI 0.81–0.95; Figure 2), indicating females had 12% lower odds of being ACPA positive than males. Both models had high heterogeneity; therefore, the reported proportions of males and females were inconsistent across studies (I^2 = 69.10% and 60.47% for RF and ACPA, respectively).

Results of the sensitivity analyses are summarized in Table 2. When excluding poor-quality studies and when only including studies published within the last 10 years, males had consistently higher odds of being RF and ACPA positive, with ORs being within the 95% CIs of the primary metaanalysis. When only including studies between the 10th and 90th percentiles for the proportion of females, and separately for the proportion of seropositive individuals, results were similar to the primary metaanalyses that included all studies. Heterogeneity for all sensitivity analyses remained high (I^2 = 50.2–70.5%).

Results when stratifying by ethnicity can be found in Table 2. For both RF and ACPA analyses, results became statistically insignificant for Asian populations and Hispanic populations. Results were consistent for White populations and heterogeneity remained high. When stratifying by institutional cohorts, results remained consistent. When stratifying by population-based cohorts, the association between sex and ACPA seropositivity became statistically insignificant (Table 2).

Random-effects metaregression results are summarized in Supplementary Table 4 (available with the online version of this article). Mean age, BMI, DAS28, HAQ-DI, and proportion of ever-smokers did not affect the relationship between sex and seropositivity for both RF and ACPA.

DISCUSSION

Whereas female sex and seropositivity have been identified as risk factors for more aggressive RA disease, this metaanalysis found that male patients with RA have higher odds of being seropositive for RF and ACPA than females. However, results were inconsistent across studies, which could be due to differences in the characteristics of the study populations.

Several prior observational studies did not report differences in seropositivity in males vs females with RA. In animal models of RA, no sex differences were identified in T cell and B cell responses to citrullinated antigens involved in the pathogenesis of RA.[101,102] ACPA was significantly more frequent in mice expressing HLA-DRB1 than wild-type control mice.[102] HLA-DRB1, which is strongly associated with ACPA in RA,[1] was more common in males than females in a population of 777 patients with RA.[91] Presence of this gene could not be considered in the metaregression analyses as it was reported in very few studies.

In addition to genetic predisposition, environmental exposures are associated with seropositivity, including smoking and obesity.[103,104] The higher rates of seropositivity in males observed in this metaanalysis could be driven by more male than female smokers. Smoking is strongly associated with developing ACPA-positive RA.[105] A metaanalysis conducted in 2010 that included 16 studies found smoking to influence RF-positive disease in males more than females.[106] A study by Lu and colleagues also found that obesity was associated with RF and ACPA in a cohort of women with RA.[107] However, we did not find that the relationship between seropositivity and smoking or obesity differed significantly by sex. Most studies included in this systematic review did not report BMI nor proportion of smokers by sex, and we may have been underpowered to detect the effect of these factors. Also, the incidence of seropositive RA has been decreasing over the past few decades in both males and females, which may be attributed to a decrease in smoking.[108]

In the general population, it has been reported that females are more likely to be seropositive for various autoantibodies (including RF but not ACPA).[109] It is possible that the autoantibodies measured in the general population are not pathogenic for autoimmune disease, hindering comparability with our study of patients with RA. Many studies included in this metaanalysis were institutional-based cohorts rather than population-based cohorts. Although mean DAS28 ranged from remission to high disease activity, the population in our metaanalysis may have included patients with more severe RA than those in population-based cohorts. Conversely, population-based cohorts are limited by potential misclassification. Both these factors can affect the seropositivity rates in studies.

A strength of this metaanalysis was that several sensitivity analyses and metaregressions were performed to determine sources of heterogeneity. Stratification by ethnicity revealed that White males were significantly more likely to be seropositive than White females. There was no significant association between sex and seropositivity in Hispanic or Asian populations. RF seropositivity has been found to differ by race/ethnicity, with White patients having the lowest prevalence and Black patients having the highest.[110] Another study reported very high rates of ACPA in an Indigenous North American population.[111] We did not identify any studies that reported the relationship between sex and seropositivity for Indigenous and Black populations.

Despite attempts to account for variations in study findings, heterogeneity remained high. Other participant characteristics, such as pollution and chemical exposures, alcohol consumption, and diet may have also driven heterogeneity, but there were insufficient data on these factors to perform analyses. Further research is required to determine factors that influence the association between sex and seropositivity.

Other limitations are that for most of the included studies, sex discrepancies in RA-associated antibodies were not the primary outcome, and data were missing with respect to potentially important confounders. In addition, we were not able to assess whether females were more likely than males to be negative for both RF and ACPA as this was generally not reported. Last,

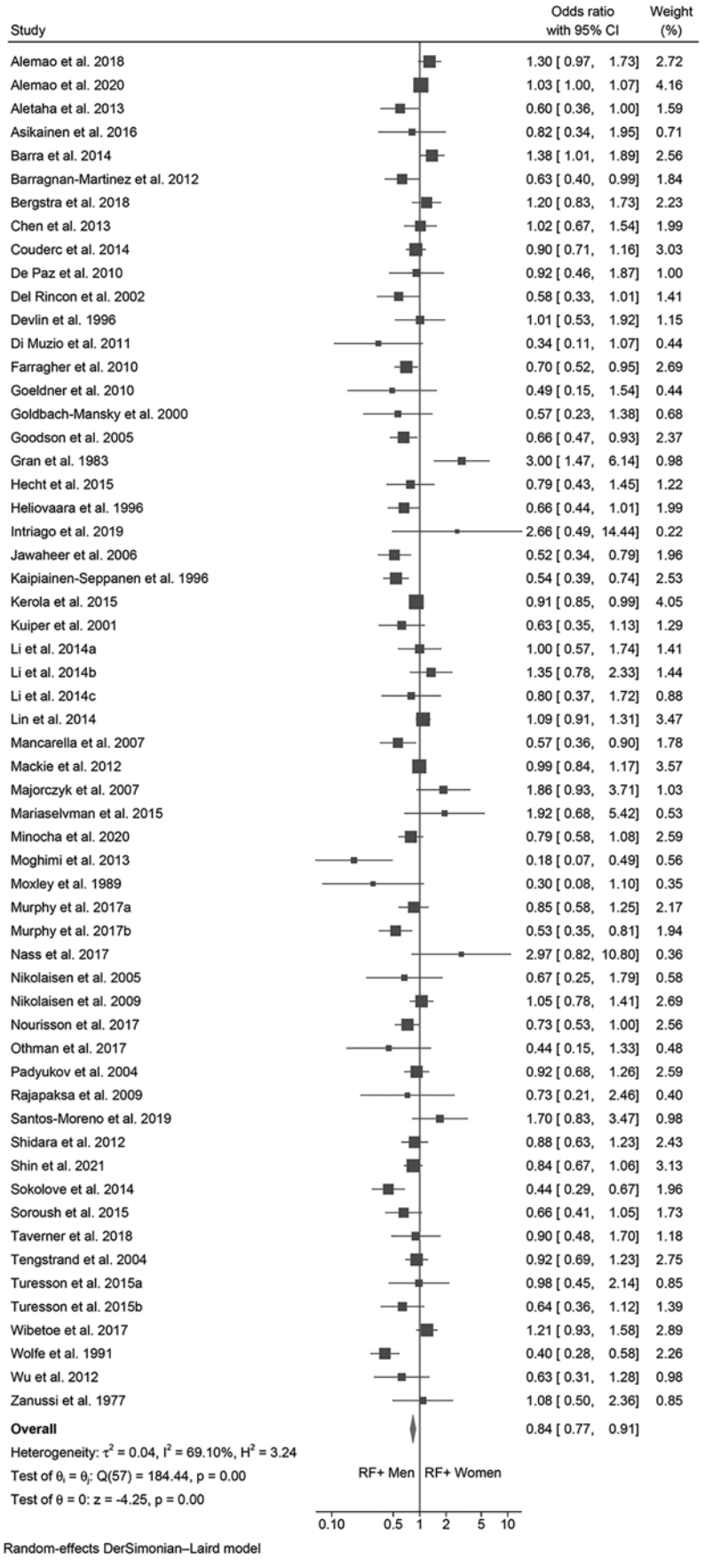

Figure 1. Metaanalysis of 55 studies reporting RF seropositivity in males and females using a random-effects model. RF: rheumatoid factor.

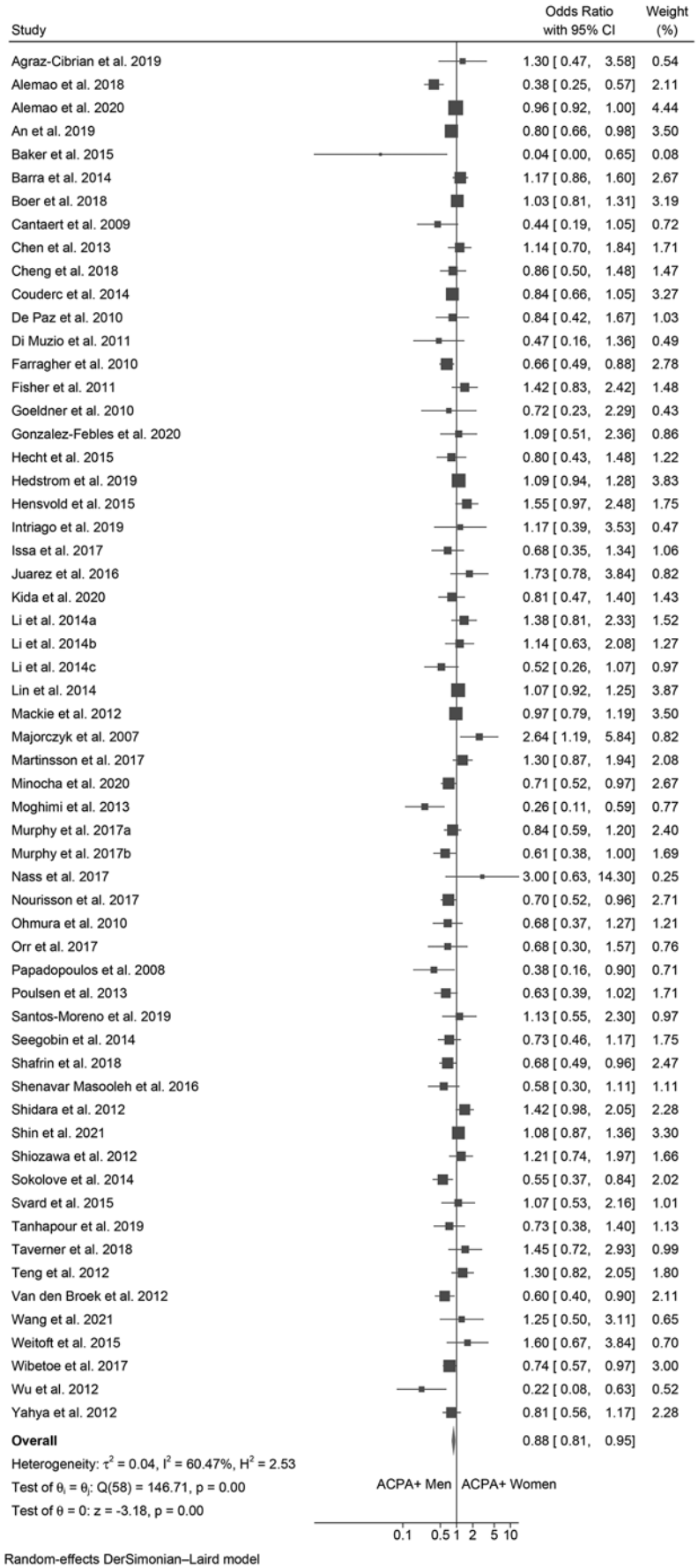

Figure 2. Metaanalysis of 56 studies reporting ACPA seropositivity in males and females using a random-effects model. ACPA: anticitrullinated protein antibody.

Table 2. Sensitivity analysis results.

Autoantibody	Studies Included	Studies Included, N	Overall OR (95% CI)	*P*	Heterogeneity, I^2, %
RF	Good- and fair-quality studies	49	0.83 (0.76–0.90)	< 0.01	70.45
	Studies published within last 10 years	36	0.91 (0.83–0.99)	0.03	64.08
	Studies within 10th to 90th percentile for % female	48	0.86 (0.79–0.93)	< 0.01	70.03
	Studies within 10th to 90th percentile for % RF+	42	0.84 (0.76–0.92)	< 0.01	62.96
	White	38	0.82 (0.74–0.90)	< 0.01	74.92
	Asian	12	0.85 (0.69–1.05)	0.13	53.00
	Hispanic	7	1.02 (0.67–1.55)	0.94	47.56
	Institutional	39	0.87 (0.77–0.98)	0.02	64.58
	Population-based	17	0.81 (0.71–0.92)	< 0.01	74.34
ACPA	Good- and fair-quality studies	47	0.88 (0.80–0.96)	< 0.01	64.83
	Studies published within last 10 years	51	0.89 (0.82–0.97)	0.01	61.53
	Studies within 10th to 90th percentile for % female	49	0.88 (0.80–0.96)	< 0.01	64.25
	Studies within 10th to 90th percentile for % ACPA+	48	0.91 (0.83–0.99)	0.03	50.21
	White	34	0.84 (0.76–0.93)	< 0.01	67.77
	Asian	17	0.91 (0.77–1.08)	0.29	56.88
	Hispanic	8	1.13 (0.84–1.54)	0.42	0.00
	Institutional	44	0.87 (0.78–0.97)	0.01	58.09
	Population-based	14	0.92 (0.80–1.06)	0.26	63.92

ACPA: anticitrullinated protein antibody; OR: odds ratio; RF: rheumatoid factor.

autoantibody titer could not be explored as few studies reported this by sex.

In this metaanalysis, males with RA were more likely to be seropositive for RF and ACPA than females. Therefore, worse RA prognosis in females cannot be attributed to more seropositive cases. Higher rates of smoking in males are likely contributing to sex differences in seropositivity rates in RA. Other factors may also affect seropositivity and future research should further explore the interaction between sex, the environment, and behaviors on antibody expression.

ONLINE SUPPLEMENT

Supplementary material accompanies the online version of this article.

REFERENCES

1. van der Woude D, van der Helm-van Mil AHM. Update on the epidemiology, risk factors, and disease outcomes of rheumatoid arthritis. Best Pract Res Clin Rheumatol 2018;32:174-87.
2. Scott DL, Wolfe F, Huizinga TW. Rheumatoid arthritis. Lancet 2010;376:1094-108.
3. Choi S, Lee KH. Clinical management of seronegative and seropositive rheumatoid arthritis: a comparative study. PLoS One 2018;13:e0195550.
4. Regueiro C, Rodriguez-Rodriguez L, Lopez-Mejias R, et al. A predominant involvement of the triple seropositive patients and others with rheumatoid factor in the association of smoking with rheumatoid arthritis. Sci Rep 2020;10:3355.
5. Sokka T, Toloza S, Cutolo M, et al. Women, men, and rheumatoid arthritis: analyses of disease activity, disease characteristics, and treatments in the QUEST-RA study. Arthritis Res Ther 2009;11:R7.
6. van den Broek M, Dirven L, Klarenbeek NB, et al. The association of treatment response and joint damage with ACPA-status in recent-onset RA: a subanalysis of the 8-year follow-up of the BeSt study. Ann Rheum Dis 2012;71:245-8.
7. Smolen JS, Landewé R, Breedveld FC, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2013 update. Ann Rheum Dis 2014;73:492-509.
8. de Punder YM, Hendrikx J, den Broeder AA, Valls Pascual E, van Riel PL, Fransen J. Should we redefine treatment targets in rheumatoid arthritis? Low disease activity is sufficiently strict for patients who are anticitrullinated protein antibody-negative. J Rheumatol 2013;40:1268-74.
9. Forslind K, Ahlmén M, Eberhardt K, Hafström I, Svensson B. Prediction of radiological outcome in early rheumatoid arthritis in clinical practice: role of antibodies to citrullinated peptides (anti-CCP). Ann Rheum Dis 2004;63:1090-5.
10. Kastbom A, Strandberg G, Lindroos A, Skogh T. Anti-CCP antibody test predicts the disease course during 3 years in early rheumatoid arthritis (the Swedish TIRA project). Ann Rheum Dis 2004;63:1085-9.
11. PROSPERO. Presence of autoantibodies in males and females with rheumatoid arthritis: a systematic review and meta-analysis. [Internet. Accessed March 11, 2022.] Available from: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42020156829
12. The Ottawa Hospital Research Institute. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. [Internet. Accessed March 11, 2022.] Available from: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp
13. Sharmin S, Kypri K, Khanam M, Wadolowski M, Bruno R, Mattick RP. Parental supply of alcohol in childhood and risky drinking in adolescence: systematic review and meta-analysis. Int J Environ Res Public Health 2017;14:287.
14. Cochrane Methods. RoB 2: a revised Cochrane risk-of-bias tool for randomized trials. [Internet. Accessed March 11, 2022.] Available from: https://methods.cochrane.org/bias/resources/rob-2-revised-cochrane-risk-bias-tool-randomized-trials
15. Szumilas M. Explaining odds ratios. J Can Acad Child Adolesc Psychiatry 2010;19:227-9.
16. Cheng J, Pullenayegum E, Marshall JK, Iorio A, Thabane L. Impact of including or excluding both-armed zero-event studies on using standard meta-analysis methods for rare event outcome: a simulation study. BMJ Open 2016;6:e010983.

17. Berkey CS, Hoaglin DC, Mosteller F, Colditz GA. A random-effects regression model for meta-analysis. Stat Med 1995;14:395-411.
18. Zanussi C, Rugarli C, Casali P, et al. Immunological status of aged subjects with reference to serological evidence of autoimmunity. Ric Clin Lab 1977;7:115-23.
19. Intriago M, Maldonado G, Cárdenas J, Ríos C. Clinical characteristics in patients with rheumatoid arthritis: differences between genders. ScientificWorldJournal 2019;2019:8103812.
20. Baker JF, Long J, Ibrahim S, Leonard MB, Katz P. Are men at greater risk of lean mass deficits in rheumatoid arthritis? Arthritis Care Res 2015;67:112-9.
21. Majorczyk E, Pawlik A, Łuszczek W, et al. Associations of killer cell immunoglobulin-like receptor genes with complications of rheumatoid arthritis. Genes Immun 2007;8:678-83.
22. Nikolaisen C, Rekvig OP, Nossent HC. Rheumatoid factor by laser nephelometry and Waaler-Rose assay: prognostic value in patients with recent-onset rheumatoid arthritis. Scand J Rheumatol 2005;34:269-76.
23. Ohmura K, Terao C, Maruya E, et al. Anti-citrullinated peptide antibody-negative RA is a genetically distinct subset: a definitive study using only bone-erosive ACPA-negative rheumatoid arthritis. Rheumatology 2010;49:2298-304.
24. Nourisson C, Soubrier M, Mulliez A, et al. Impact of gender on the response and tolerance to abatacept in patients with rheumatoid arthritis: results from the 'ORA' registry. RMD Open 2017;3:e000515.
25. Wolfe F, Cathey MA, Roberts FK. The latex test revisited. Rheumatoid factor testing in 8,287 rheumatic disease patients. Arthritis Rheum 1991;34:951-60.
26. Hedström AK, Hössjer O, Klareskog L, Alfredsson L. Interplay between alcohol, smoking and HLA genes in RA aetiology. RMD Open 2019;5:e000893.
27. de Paz B, Alperi-López M, Ballina-García FJ, et al. Interleukin 10 and tumor necrosis factor-alpha genotypes in rheumatoid arthritis--association with clinical response to glucocorticoids. J Rheumatol 2010;37:503-11.
28. Soroush M, Taghipour MA, Soroosh S. Comparison of clinical course, manifestations and symptoms of rheumatoid arthritis between men and women referred to two medical centers in Tehran. Biosci Biotechnol Res Asia 2015;12:203-8.
29. Fisher BA, Plant D, Brode M, et al. Antibodies to citrullinated α-enolase peptide 1 and clinical and radiological outcomes in rheumatoid arthritis. Ann Rheum Dis 2011;70:1095-8.
30. Couderc M, Gottenberg JE, Mariette X, et al; Club Rhumatismes et Inflammations. Influence of gender on response to rituximab in patients with rheumatoid arthritis: results from the Autoimmunity and Rituximab registry. Rheumatology 2014;53:1788-93.
31. Turesson C, Bergström U, Pikwer M, Nilsson J, Jacobsson LT. High serum cholesterol predicts rheumatoid arthritis in women, but not in men: a prospective study. Arthritis Res Ther 2015;17:284.
32. An J, Bider-Canfield Z, Kang J, et al. Economic evaluation of anticyclic citrullinated peptide positivity in rheumatoid arthritis. J Manag Care Spec Pharm 2019;25:469-77.
33. Mancarella L, Bobbio-Pallavicini F, Ceccarelli F, et al; GISEA group. Good clinical response, remission, and predictors of remission in rheumatoid arthritis patients treated with tumor necrosis factor-alpha blockers: the GISEA study. J Rheumatol 2007; 34:1670-3.
34. Padyukov L, Silva C, Stolt P, Alfredsson L, Klareskog L. A gene-environment interaction between smoking and shared epitope genes in HLA-DR provides a high risk of seropositive rheumatoid arthritis. Arthritis Rheum 2004;50:3085-92.
35. Jawaheer D, Lum RF, Gregersen PK, Criswell LA. Influence of male sex on disease phenotype in familial rheumatoid arthritis. Arthritis Rheum 2006;54:3087-94.
36. Shidara K, Inoue E, Hoshi D, et al. Anti-cyclic citrullinated peptide antibody predicts functional disability in patients with rheumatoid arthritis in a large prospective observational cohort in Japan. Rheumatol Int 2012;32:361-6.
37. Shenavar Masooleh I, Hajiabbasi A, Zayeni H, et al. Anticyclic citrullinated peptide antibody in rheumatoid arthritis:a cross-sectional study in Iran. Turk J Med Sci 2016;46:1309-13.
38. Rajapaksa GK, De Silva V, Goonathilake S, Athukorala I, Wijayarathna LS, Udagama-Randeniya PV. A study of immunological profile, disease characteristics and socioeconomic status of a population of rheumatoid arthritis patients in Sri Lanka. Indian J Rheumatol 2009;4:3-10.
39. Tengstrand B, Ahlmén M, Hafström I. The influence of sex on rheumatoid arthritis: a prospective study of onset and outcome after 2 years. J Rheumatol 2004;31:214-22.
40. Teng E, Leong KP, Li HH, et al; TTSH RA Study Group. Analysis of a genome-wide association study-linked locus (CCR6) in Asian rheumatoid arthritis. DNA Cell Biol 2012;31:607-10.
41. Tanhapour M, Shahmohamadnejad S, Vaisi-Raygani A, et al. Association between activity and genotypes of paraoxonase1 $L_{55}M$ (rs854560) increases the disease activity of rheumatoid arthritis through oxidative stress. Mol Biol Rep 2019;46:741-9.
42. Papadopoulos NG, Tsiaousis GZ, Pavlitou-Tsiontsi A, Giannakou A, Galanopoulou VK. Does the presence of anti-CCP autoantibodies and their serum levels influence the severity and activity in rheumatoid arthritis patients? Clin Rev Allergy Immunol 2008;34:11-5.
43. Alemao E, Guo Z, Frits ML, Iannaccone CK, Shadick NA, Weinblatt ME. Association of anti-cyclic citrullinated protein antibodies, erosions, and rheumatoid factor with disease activity and work productivity: a patient registry study. Semin Arthritis Rheum 2018;47:630-8.
44. Barra L, Pope JE, Orav JE, et al; CATCH Investigators. Prognosis of seronegative patients in a large prospective cohort of patients with early inflammatory arthritis. J Rheumatol 2014;41:2361-9.
45. Shiozawa K, Kawasaki Y, Yamane T, et al. Anticitrullinated protein antibody, but not its titer, is a predictor of radiographic progression and disease activity in rheumatoid arthritis. J Rheumatol 2012;39:694-700.
46. Chen Y, Yu Z, Packham JC, Mattey DL. Influence of adult height on rheumatoid arthritis: association with disease activity, impairment of joint function and overall disability. PLoS One 2013;8:e64862.
47. Farragher TM, Lunt M, Plant D, Bunn DK, Barton A, Symmons DP. Benefit of early treatment in inflammatory polyarthritis patients with anti-cyclic citrullinated peptide antibodies versus those without antibodies. Arthritis Care Res 2010;62:664-75.
48. Seegobin SD, Ma MH, Dahanayake C, et al. ACPA-positive and ACPA-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.
49. Moghimi J, Ghorbani R, Hasani F, Sheikhvatan M. Discriminative and diagnostic value of anti-cyclic citrullinated peptide antibodies in Iranian patients with rheumatoid arthritis. Rheumatol Int 2013;33:601-5.
50. Bergstra SA, Allaart CF, Ramiro S, et al. Sex-associated treatment differences and their outcomes in rheumatoid arthritis: results from the METEOR register. J Rheumatol 2018;45:1361-6.
51. Turesson C, Bergström U, Pikwer M, Nilsson J, Jacobsson LT. A high body mass index is associated with reduced risk of rheumatoid arthritis in men, but not in women. Rheumatology 2016;55:307-14.
52. Murphy D, Mattey D, Hutchinson D. Anti-citrullinated protein antibody positive rheumatoid arthritis is primarily determined by

rheumatoid factor titre and the shared epitope rather than smoking per se. PLoS One 2017;12:e0180655.
53. Heliövaara M, Aho K, Knekt P, Reunanen A, Aromaa A. Serum cholesterol and risk of rheumatoid arthritis in a cohort of 52 800 men and women. Br J Rheumatol 1996;35:255-7.
54. Wu XY, Guo JP, Yin FR, et al. Macrophage-inducible C-type lectin is associated with anti-cyclic citrullinated peptide antibodies-positive rheumatoid arthritis in men. Chin Med J 2012;125:3115-9.
55. Orr C, Najm A, Biniecka M, et al. Synovial immunophenotype and anti-citrullinated peptide antibodies in rheumatoid arthritis patients: relationship to treatment response and radiologic prognosis. Arthritis Rheumatol 2017;69:2114-23.
56. Devlin J, Lilley J, Gough A, et al. Clinical associations of dual-energy X-ray absorptiometry measurement of hand bone mass in rheumatoid arthritis. Br J Rheumatol 1996;35:1256-62.
57. 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.
58. Nikolaisen C, Kvien TK, Mikkelsen K, Kaufmann C, Rødevand E, Nossent JC. Contemporary use of disease-modifying drugs in the management of patients with early rheumatoid arthritis in Norway. Scand J Rheumatol 2009;38:240-5.
59. Santos-Moreno P, Sánchez G, Castro C. Rheumatoid factor as predictor of response to treatment with anti-TNF alpha drugs in patients with rheumatoid arthritis: results of a cohort study. Medicine 2019;98:e14181.
60. Lin J, Liu C, Yang B, Ou Q. Age-related diagnostic utility of rheumatoid factor, anticyclic citrullinated peptide and antikeratin antibodies in Chinese patients with rheumatoid arthritis. J Int Med Res 2014;42:711-7.
61. Issa SF, Christensen AF, Lindegaard HM, et al. Galectin-3 is persistently increased in early rheumatoid arthritis (RA) and associates with anti-CCP seropositivity and MRI bone lesions, while early fibrosis markers correlate with disease activity. Scand J Immunol 2017;86:471-8.
62. Li C, Mu R, Guo J, et al. Genetic variant in IL33 is associated with susceptibility to rheumatoid arthritis. Arthritis Res Ther 2014;16:R105.
63. Othman MA, Ghazali WSW, Hamid W, Wong KK, Yahya NK. Anti-carbamylated protein antibodies in rheumatoid arthritis patients and their association with rheumatoid factor. Saudi Med J 2017;38:934-41.
64. Kerola AM, Nieminen TV, Virta LJ, et al. No increased cardiovascular mortality among early rheumatoid arthritis patients: a nationwide register study in 2000-2008. Clin Exp Rheumatol 2015;33:391-8.
65. Barragán-Martínez C, Amaya-Amaya J, Pineda-Tamayo R, et al. Gender differences in Latin-American patients with rheumatoid arthritis. Gend Med 2012;9:490-510.e5.
66. Martinsson K, Johansson A, Kastbom A, Skogh T. Immunoglobulin (Ig)G1 and IgG4 anti-cyclic citrullinated peptide (CCP) associate with shared epitope, whereas IgG2 anti-CCP associates with smoking in patients with recent-onset rheumatoid arthritis (the Swedish TIRA project). Clin Exp Immunol 2017;188:53-62.
67. Goodson N, Marks J, Lunt M, Symmons D. Cardiovascular admissions and mortality in an inception cohort of patients with rheumatoid arthritis with onset in the 1980s and 1990s. Ann Rheum Dis 2005;64:1595-601.
68. Boer AC, Boonen A, van der Helm van Mil AHM. Is anti-citrullinated protein antibody-positive rheumatoid arthritis still a more severe disease than anti-citrullinated protein antibody-negative rheumatoid arthritis? A longitudinal cohort study in rheumatoid arthritis patients diagnosed from 2000 onward. Arthritis Care Res 2018;70:987-96.
69. Poulsen CH, Jacobsen S, Frisch M, Frederiksen K, Johansen C. Anti-cyclic citrullinated peptide antibodies do not reflect self-reported disability and physical health in patients with rheumatoid arthritis of less than 5 years of duration. Rheumatol Int 2013;33:2763-72.
70. Asikainen J, Nikiphorou E, Kaarela K, et al. Is long-term radiographic joint damage different between men and women? Prospective longitudinal data analysis of four early RA cohorts with greater than 15 years follow-up. Clin Exp Rheumatol 2016; 34:641-5.
71. Nass FR, Skare TL, Goeldner I, Nisihara R, Messias-Reason IT, Utiyama SRR. Analysis of four serum biomarkers in rheumatoid arthritis: association with extra articular manifestations in patients and arthralgia in relatives. Rev Bras Reumatol Engl Ed 2017; 57:286-93.
72. Weitoft T, Larsson A, Manivel VA, Lysholm J, Knight A, Rönnelid J. Cathepsin S and cathepsin L in serum and synovial fluid in rheumatoid arthritis with and without autoantibodies. Rheumatology 2015;54:1923-8.
73. Kaipiainen-Seppänen O, Aho K, Isomäki H, Laakso M. Incidence of rheumatoid arthritis in Finland during 1980-1990. Ann Rheum Dis 1996;55:608-11.
74. Goeldner I, Skare TL, de Messias Reason IT, Nisihara RM, Silva MB, Utiyama SR. Anti-cyclic citrullinated peptide antibodies and rheumatoid factor in rheumatoid arthritis patients and relatives from Brazil. Rheumatology 2010;49:1590-3.
75. Hecht C, Englbrecht M, Rech J, et al. Additive effect of anti-citrullinated protein antibodies and rheumatoid factor on bone erosions in patients with RA. Ann Rheum Dis 2015;74:2151-6.
76. Svärd A, Skogh T, Alfredsson L, et al. Associations with smoking and shared epitope differ between IgA- and IgG-class antibodies to cyclic citrullinated peptides in early rheumatoid arthritis. Arthritis Rheumatol 2015;67:2032-7.
77. Cantaert T, Brouard S, Thurlings RM, et al. Alterations of the synovial T cell repertoire in anti-citrullinated protein antibody-positive rheumatoid arthritis. Arthritis Rheum 2009;60:1944-56.
78. Di Muzio G, Perricone C, Ballanti E, et al. Complement system and rheumatoid arthritis: relationships with autoantibodies, serological, clinical features, and anti-TNF treatment. Int J Immunopathol Pharmacol 2011;24:357-66.
79. Kuiper S, van Gestel AM, Swinkels HL, de Boo TM, da Silva JA, van Riel PL. Influence of sex, age, and menopausal state on the course of early rheumatoid arthritis. J Rheumatol 2001;28:1809-16.
80. Juarez M, Bang H, Hammar F, et al. Identification of novel antiacetylated vimentin antibodies in patients with early inflammatory arthritis. Ann Rheum Dis 2016;75:1099-107.
81. Wibetoe G, Ikdahl E, Rollefstad S, et al. Cardiovascular disease risk profiles in inflammatory joint disease entities. Arthritis Res Ther 2017;19:153.
82. Shafrin J, Tebeka MG, Price K, Patel C, Michaud K. The economic burden of ACPA-positive status among patients with rheumatoid arthritis. J Manag Care Spec Pharm 2018;24:4-11.
83. Hensvold AH, Magnusson PK, Joshua V, et al. Environmental and genetic factors in the development of anticitrullinated protein antibodies (ACPAs) and ACPA-positive rheumatoid arthritis: an epidemiological investigation in twins. Ann Rheum Dis 2015;74:375-80.
84. Aletaha D, Alasti F, Smolen JS. Rheumatoid factor determines structural progression of rheumatoid arthritis dependent and independent of disease activity. Ann Rheum Dis 2013;72:875-80.
85. Cheng TT, Yu SF, Su FM, et al. Anti-CCP-positive patients with RA

have a higher 10-year probability of fracture evaluated by FRAX®: a registry study of RA with osteoporosis/fracture. Arthritis Res Ther 2018;20:16.
86. Mackie SL, Taylor JC, Martin SG, et al. A spectrum of susceptibility to rheumatoid arthritis within HLA-DRB1: stratification by autoantibody status in a large UK population. Genes Immun 2012;13:120-8.
87. Moxley G. Immunoglobulin kappa genotype confers risk of rheumatoid arthritis among HLA-DR4 negative individuals. Arthritis Rheum 1989;32:1365-70.
88. Goldbach-Mansky R, Lee J, McCoy A, et al. Rheumatoid arthritis associated autoantibodies in patients with synovitis of recent onset. Arthritis Res 2000;2:236-43.
89. Sokolove J, Johnson DS, Lahey LJ, et al. Rheumatoid factor as a potentiator of anti-citrullinated protein antibody-mediated inflammation in rheumatoid arthritis. Arthritis Rheumatol 2014;66:813-21.
90. Gran JT, Husby G, Thorsby E. The association between rheumatoid arthritis and the HLA antigen DR4. Ann Rheum Dis 1983; 42:292-6.
91. del Rincón I, Battafarano DF, Arroyo RA, Murphy FT, Escalante A. Heterogeneity between men and women in the influence of the HLA-DRB1 shared epitope on the clinical expression of rheumatoid arthritis. Arthritis Rheum 2002;46:1480-8.
92. Mariaselvam CM, Chaaben AB, Salah S, et al. Human leukocyte antigen-G polymorphism influences the age of onset and autoantibody status in rheumatoid arthritis. Tissue Antigens 2015;85:182-9.
93. Taverner D, Vallvé JC, Ferré R, Paredes S, Masana L, Castro A. Variables associated with subclinical atherosclerosis in a cohort of rheumatoid arthritis patients: sex-specific associations and differential effects of disease activity and age. PLoS One 2018;13:e0193690.
94. Agraz-Cibrián JM, Espinoza-De León GN, Durán-Avelar MJ, et al. The TNFA -857C/T polymorphism: association with rheumatoid arthritis and anti-CCP levels in a Mexican population. J Immunol Res 2019;2019:2637607.
95. Alemao E, Bao Y, Weinblatt ME, Shadick N. Association of seropositivity and mortality in rheumatoid arthritis and the impact of treatment with disease-modifying antirheumatic drugs: results from a real-world study. Arthritis Care Res 2020;72:176-83.
96. González-Febles J, Rodríguez-Lozano B, Sánchez-Piedra C, et al. Association between periodontitis and anti-citrullinated protein antibodies in rheumatoid arthritis patients: a cross-sectional study. Arthritis Res Ther 2020;22:27.
97. Kida D, Takahashi N, Kaneko A, et al. A retrospective analysis of the relationship between anti-cyclic citrullinated peptide antibody and the effectiveness of abatacept in rheumatoid arthritis patients. Sci Rep 2020;10:19717.
98. Minocha A, Kukran S, Yee P, Nisar M. The differential effect of antibodies on radiographic progression in rheumatoid arthritis. Mediterr J Rheumatol 2020;31:393-9.
99. Shin S, Park EH, Kang EH, Lee YJ, Song YW, Ha YJ. Sex differences in clinical characteristics and their influence on clinical outcomes in an observational cohort of patients with rheumatoid arthritis. Joint Bone Spine 2021;88:105124.
100. Wang X, Sun L, He N, et al. Increased expression of CXCL2 in ACPA-positive rheumatoid arthritis and its role in osteoclastogenesis. Clin Exp Immunol 2021;203:194-208.
101. Taneja V, Behrens M, Mangalam A, Griffiths MM, Luthra HS, David CS. New humanized HLA-DR4-transgenic mice that mimic the sex bias of rheumatoid arthritis. Arthritis Rheum 2007;56:69-78.
102. Cairns E, Saunders S, Bell DA, Blackler G, Lac P, Barra L. The effect of sex on immune responses to a homocitrullinated peptide in the DR4-transgenic mouse model of rheumatoid arthritis. J Transl Autoimmun 2020;3:100053.
103. Marchand NE, Sparks JA, Tedeschi SK, et al. Abdominal obesity in comparison with general obesity and risk of developing rheumatoid arthritis in women. J Rheumatol 2021;48:165-73.
104. Rantapää Dahlqvist S, Andrade F. Individuals at risk of seropositive rheumatoid arthritis: the evolving story. J Intern Med 2019; 286:627-43.
105. Smolen JS, Aletaha D, Barton A, et al. Rheumatoid arthritis. Nat Rev Dis Primers 2018;4:18001.
106. Sugiyama D, Nishimura K, Tamaki K, et al. Impact of smoking as a risk factor for developing rheumatoid arthritis: a meta-analysis of observational studies. Ann Rheum Dis 2010;69:70-81.
107. Lu B, Hiraki LT, Sparks JA, et al. Being overweight or obese and risk of developing rheumatoid arthritis among women: a prospective cohort study. Ann Rheum Dis 2014;73:1914-22.
108. Myasoedova E, Davis J, Matteson EL, Crowson CS. Is the epidemiology of rheumatoid arthritis changing? Results from a population-based incidence study, 1985-2014. Ann Rheum Dis 2020;79:440-4.
109. Dillon CF, Weisman MH, Miller FW. Population-based estimates of humoral autoimmunity from the U.S. National Health and Nutrition Examination Surveys, 1960-2014. PLoS One 2020;15:e0226516.
110. Greenberg JD, Spruill TM, Shan Y, et al. Racial and ethnic disparities in disease activity in patients with rheumatoid arthritis. Am J Med 2013;126:1089-98.
111. Ioan-Facsinay A, Willemze A, Robinson DB, et al. Marked differences in fine specificity and isotype usage of the anti-citrullinated protein antibody in health and disease. Arthritis Rheum 2008;58:3000-8.