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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,

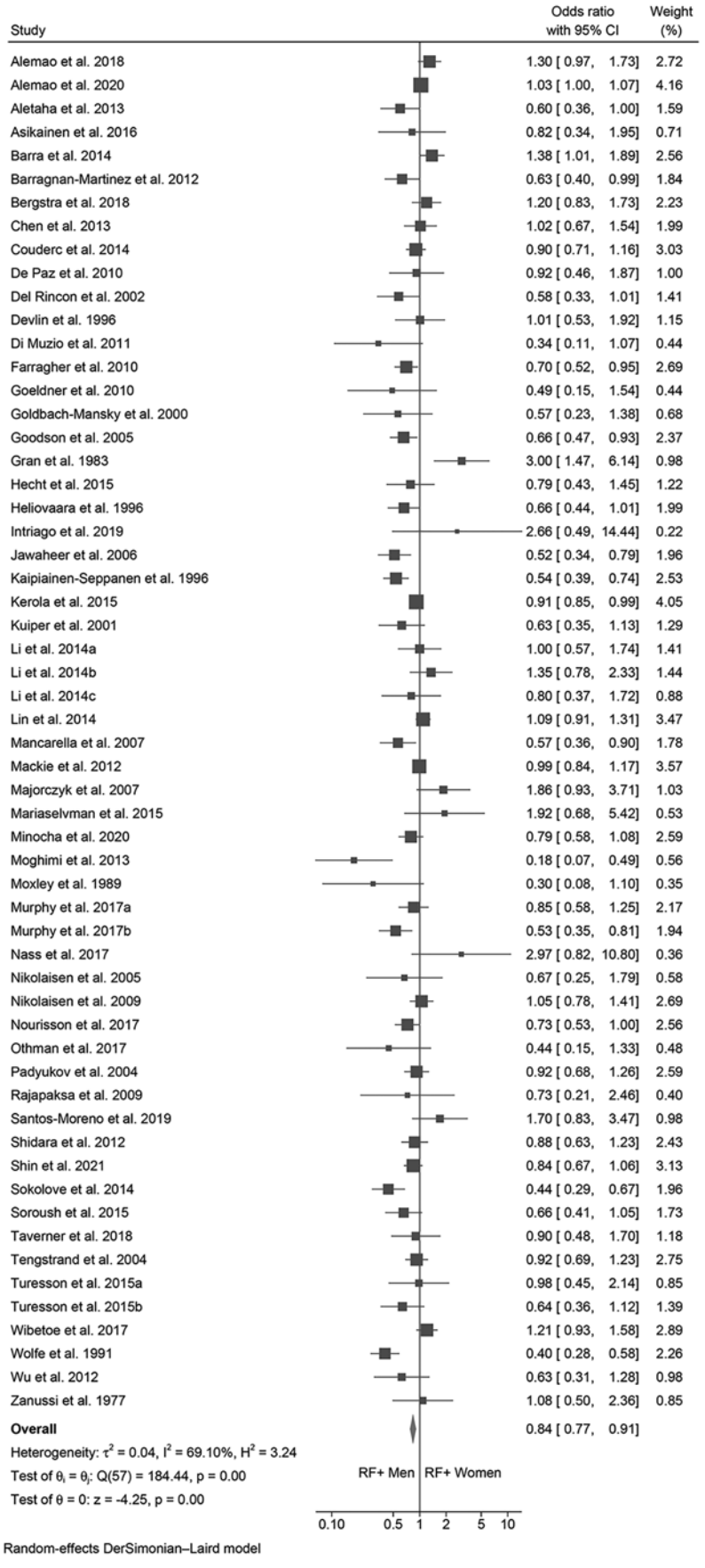

Figure 1. Metaanalysis of 55 studies reporting RF seropositivity in males and females using a random-effects model. RF: rheumatoid factor.

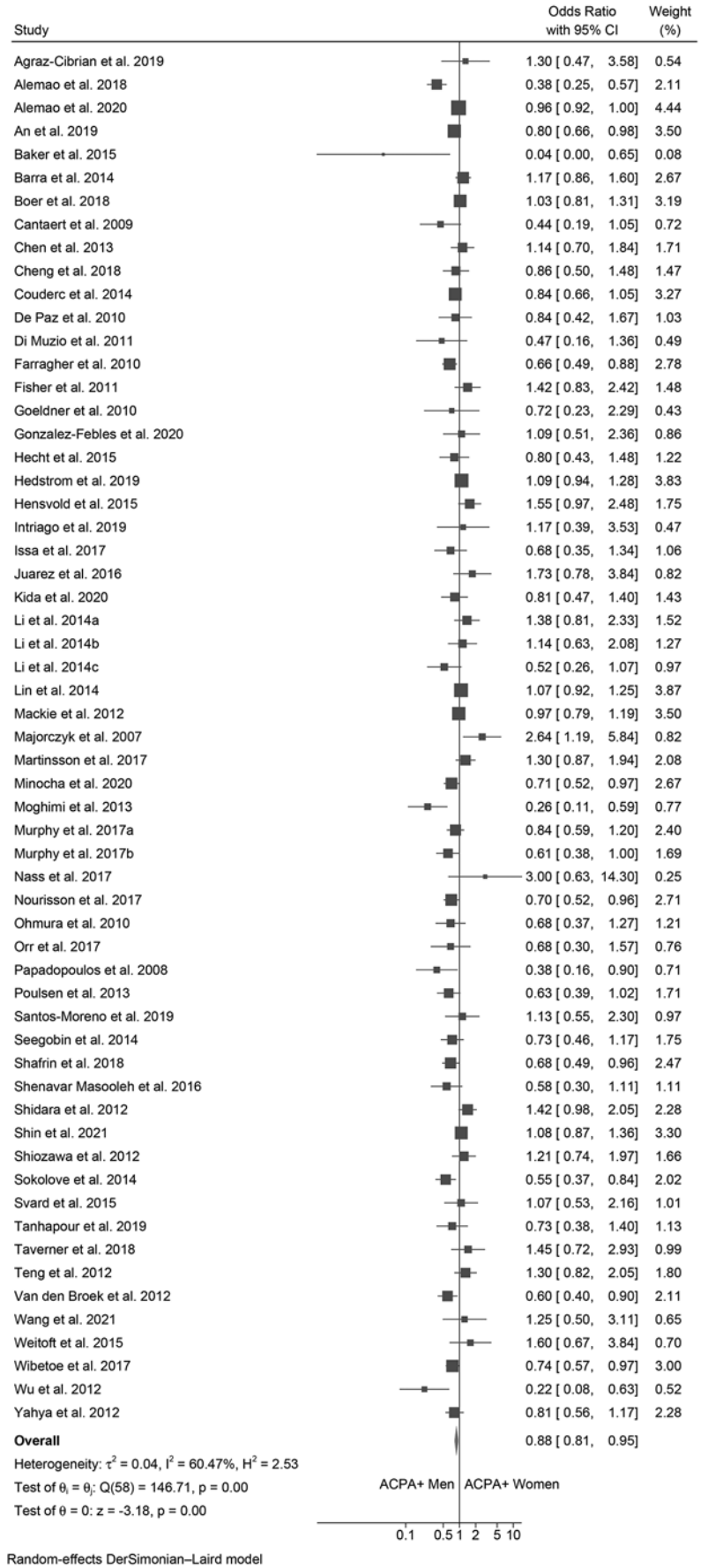

Figure 2. Metaanalysis of 56 studies reporting ACPA seropositivity in males and females using a random-effects model. ACPA: anticitrullinated protein antibody.

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.

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