

ORIGINAL RESEARCH

Allergic conditions and risk of
rheumatoid arthritis: a Swedish case-
control study

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ABSTRACT

Objective To determine the association of allergic conditions with incident rheumatoid arthritis (RA), especially in relation to smoking history and anti-citrullinated peptide antibody (ACPA) status.

Methods This case-control study included 3515 incident RA cases and 5429 matched controls from the Epidemiological Investigation of Rheumatoid Arthritis study 1995 to 2016, including questionnaire-based information on eight allergic conditions composed from a list of 59 unique allergies. We used logistic regression and adjusted ORs (aOR) to assess the association between allergic conditions and risk of RA, adjusting for age, sex, residential area, body mass index, education, and smoking, and stratified by smoking and ACPA.

Results A history of any reported allergy was equally common in RA (n=1047, 30%) as among population controls (n=1540, 29%), aOR 1.04, 95% CI 0.95 to 1.15. Metal, respiratory, food, plant/pollen and chemical allergies were not associated with risk of RA. By contrast, statistically significant associations were observed for animal dander allergy (6% vs 5%, aOR 1.37, 95% CI 1.03 to 1.82), especially in ACPA-positive RA (aOR 1.46 95% CI 1.06 to 2.01) and for atopic dermatitis, in particular for older and ACPA-negative RA (aOR 2.33, 95% CI 1.37 to 3.96 at age 80). Never smokers with allergic rhinitis also had increased risk of developing RA (aOR 1.30, 95% CI 1.00 to 1.68).

Conclusion Most common allergies do not increase risk of RA, nor do they protect against RA. However, some allergic conditions, notably animal dander allergy, atopic dermatitis and allergic rhinitis, were associated with an increased risk for RA.

INTRODUCTION

Increasing evidence suggests that rheumatoid arthritis (RA) may originate in mucosal sites such as the lungs and oral cavity. Smoking is a strong risk factor for RA, and is believed to trigger RA through generation of anti-citrullinated peptide antibodies (ACPA).^{1 2} Asthma has been shown to be associated with RA in several studies,³⁻⁸ at least in never smokers.^{9 10} Two recent retrospective studies

Key messages**What is already known about this subject?**

► Some studies have suggested an association between atopic diseases and rheumatoid arthritis (RA).

What does this study add?

- Most of the allergic conditions studied, including food allergies, were not associated with increased risk of RA.
- However, we identified animal dander as a novel risk factor for RA—especially anticitrullinated peptide antibody (ACPA)-positive RA.
- Atopic dermatitis was associated with RA in ACPA-negative RA and/or older adults, and allergic rhinitis was associated with increased risk of RA in never smokers.

How might this impact on clinical practice or further developments?

- Based on these findings, clinicians can reassure patients that allergic conditions do not highly increase risk of RA, though reducing animal dander exposure might be helpful for those at highest risk.

have also demonstrated an association between atopic diseases and incident RA,^{3 6} one using self-reported definition of allergies³ and the other using diagnosis codes.⁶ In the latter, the association between allergies and RA was stronger with history of more than one allergic disease.⁶ These findings call for assessments of atopic disease in relation to smoking and ACPA status. They also raise the question of whether other allergic conditions, such as allergic rhinitis, contact and food allergies, also increase RA risk.

Food allergies have been linked with RA by historical case reports of RA sustained remission after food allergy treatment,^{11 12} a study of rats showing increased egg and milk IgE in rats with RA¹³ and a recent retrospective case-control study using self-reported food

allergy.³ However, another study that measured food allergy by skin prick test showed no association with RA.¹⁴ Similarly, another study showed no association of grass allergy assessed by skin prick test with RA.^{14,15} Additional but limited evidence from retrospective studies shows no association between self-reported allergy to grass,³ house mites,¹⁶ pets³ or insects³ with RA. Other allergy types such as metal and chemical allergies have not been studied.

To address these gaps, we leveraged Epidemiological Investigation of Rheumatoid Arthritis (EIRA), a population-based study of incident RA in Sweden¹⁷ to determine the relationship between allergic conditions and risk of RA, taking smoking and ACPA status into account.

METHODS

Study design

This case–control study involved 3515 incident RA cases and 5429 controls recruited to the EIRA study between 1995 and 2016, within 1 year since RA symptom onset. Controls were randomly selected from the national population and matched 1:1 until 2005 and thereafter 2:1 on age, sex and residential area. All participants completed a questionnaire at the time of enrolment, along with written informed consent. Response rate for the first phase of EIRA (until 2005) was 96% for cases and 82% for controls as described previously.¹⁸ Response rate for the second phase of EIRA (since 2005) is 91% for cases and 69% for controls.

Exposure (allergic conditions)

Participants self-reported allergic conditions from a list of 59 potential allergic exposures on the EIRA enrolment questionnaire. The questionnaire specifically asked whether they had history of hay fever (allergic rhinitis) or eczema (atopic dermatitis). The remaining allergy types were reported from a list of options, but only on the questionnaires administered 2005 and prior. We combined these 59 options into six additional allergy categories. Animal dander allergy asked if the participant had any fur allergies (including cat). Metal allergies included nickel, cobalt, chrome, silver or gold. Respiratory allergies included any report of effort asthma, non-exertional asthma, cold asthma, non-allergic asthma or ‘other allergic airway disease’. Food allergies included any report of allergy to seafood, kernel fruits/nuts, gluten, citrus, fruits/vegetables, eggs, chocolate, lactose, alcohol, milk, poultry, wine/liquor, fish, soy, rye, blue cheese or legumes. Plant/pollen allergies included pollen, flowers, fir, mould, eucalyptus or hyacinth allergies. Chemical allergies included cosmetics, perfume, ink, solvent, tobacco smoke, detergent, skin cream, shampoo, plastic, ‘various chemicals’, plaster, rubber, amalgam, ammonia, latex, charcoal, cement, conditioner, concrete colour, chlorine, dish soap, hair dye, or formaldehyde. To reflect an ‘allergic phenotype’ across conditions, we created an ‘any allergy’ (yes/no) variable combining presence of

any above the allergic exposures. We also created a variable quantifying the number of reported allergic conditions (categorised as 0, 1, 2, 3+) out of the 59 potential allergic exposures.

Outcome (RA)

Inclusion criteria for EIRA included adults age 18 years or older with RA diagnosed for the first time. Exclusion criteria included inability to speak Swedish and age >70 years (until 2009). All RA cases were examined and diagnosed by a rheumatologist at the time of enrolment and fulfilled American College of Rheumatology/EULAR 1987 or 2010 criteria for RA.^{19,20} ACPA status was determined using the commercial CCP2 diagnostic kit from Eurodiagnostica for frozen baseline sera from EIRA patients, while rheumatoid factor (RF) status was determined at inclusion by the recruiting site. RA cases could have positive ACPA, RF or both.

Covariates

Covariates including age, sex, residential area (ten geographic areas), body mass index (BMI), educational level (compulsory school only, upper secondary school or university degree) and smoking (never, non-regular, past and current) were self-reported by participants at the time of the EIRA enrolment questionnaire. ‘Ever’ smokers included non-regular, past and current smokers.

Statistical analysis

χ^2 tests compared proportions, and Wilcoxon rank-sum tests with medians and IQR compared continuous variables. We performed separate, unconditional logistic regression models of each allergic condition to obtain adjusted ORs (aOR) for all RA, ACPA-positive RA and ACPA-negative RA, adjusting for age, sex, residential area, BMI, education, and smoking (never, non-regular, past and current). Appropriately powered logistic regression models require at least 70 events for this number of covariates,²¹ which was easily met by the 3515 RA cases in this study. For each allergic condition, we also tested interactions with age, sex, and smoking because of observed differences in RA phenotypes by these variables and included them in the model if they were statistically significant ($p < 0.05$). We then repeated all models for RF-positive RA. Finally, we evaluated the duration (in years) that any allergy overall occurred before RA as a predictor of RA. Only 111 (1.24%) of the participants were missing data for one or more of the covariates (age, sex, residential area, BMI, education or smoking), and these participants were excluded from further analysis. All analyses were prespecified in a protocol and performed using SAS V.9.4 (SAS Institute).

RESULTS

Among the 3515 RA cases included in this study, median age was 55 (IQR 45–63) years, 71% were female, 2262 (66%) were positive for ACPA and 2301 (66%) were positive for RF. Compared with their 5429 matched controls,

Table 1 Characteristics of the EIRA RA cases from 1995 to 2016 and population controls at enrolment questionnaire

Characteristic	RA cases (N=3515)	Controls (N=5429)	Adjusted OR* for all RA (95% CI)
Age, years, median (Q1,Q3)	55 (45,63)	56 (44,63)	1.00 (0.99 to 1.00)
Female sex, N (%)	2493 (71)	3838 (71)	1.05 (0.95 to 1.16)
BMI, kg/m ² , N (%)			
<20	252 (7)	320 (6)	1.23 (1.03 to 1.48)
20–25	1574 (45)	2576 (48)	(ref)
25–30	1178 (34)	1811 (34)	1.04 (0.94 to 1.15)
30+	502 (14)	699 (13)	1.12 (0.98 to 1.28)
Educational level, N (%)			
Compulsory school only	876 (25)	1043 (19)	(ref)
Upper secondary school	1803 (51)	2649 (49)	0.80 (0.71 to 0.89)
University degree	835 (24)	1730 (32)	0.61 (0.53 to 0.69)
Smoking status, N (%)			
Never smoker	1146 (33)	2413 (45)	(ref)
Non-regular smoker	287 (8)	478 (9)	1.26 (1.07 to 1.49)
Past smoker	1146 (33)	1562 (29)	1.56 (1.40 to 1.73)
Current smoker	915 (27)	924 (17)	1.95 (1.73 to 2.19)

*Adjusting for age, sex, BMI, education, smoking. Bold values are statistically significant (p<0.05). BMI, body mass index; EIRA, Epidemiological Investigation of Rheumatoid Arthritis; RA, rheumatoid arthritis.

RA cases had lower BMI and educational level, and were more often smokers (table 1).

A total of 1047 (30%) of RA cases and 1540 (29%) of the controls reported a history of at least one of the allergies studied, with 226 (6%) RA cases and 382 (7%) controls reporting two allergic conditions and 140 (4%) RA cases and 208 (4%) controls reporting three or more. The most common allergic conditions were atopic dermatitis (11% of cases and 10% of controls), plant/pollen allergies (9% of cases and 10% of controls), and allergic rhinitis (9% of cases and 8% of controls) (table 2).

After adjustment, a history of any allergic condition was not associated with risk of RA (aOR 1.04, 95% CI 0.95 to 1.15). Having two (aOR 0.93, 95% CI 0.78 to 1.11) or three or more (aOR 1.05, 95% CI 0.84 to 1.32) allergic conditions was also not associated with increased risk of RA. Metal, respiratory, food, plant/pollen and chemical allergies were not associated with RA (table 2). Animal dander was the only allergy associated with risk of RA overall, and mostly for ACPA positive RA (table 2). In addition, atopic dermatitis was associated with increased risk of ACPA-negative RA (aOR 1.32, 95% CI 1.06 to

Table 2 Association between types of allergies and risk of RA among the 3515 EIRA cases diagnosed with RA between 1995 and 2016 and and their 5429 controls

Allergy type	No (%)		Adjusted* OR (95% CI)		
	RA cases (N=3515)	Controls (N=5429)	All RA (N=3515)	ACPA +RA (N=2262)	ACPA- RA (N=1165)
Animal dander†	89 (6)	134 (5)	1.37 (1.03 to 1.82)	1.46 (1.06 to 2.01)	1.17 (0.73 to 1.88)
Allergic rhinitis	270 (9)	387 (8)	1.30 (1.00 to 1.68)‡	1.24 (0.90 to 1.70)‡	1.39 (0.97 to 2.00)‡
Atopic dermatitis	345 (11)	453 (10)	1.16 (0.98 to 1.25)§*	0.99 (0.83 to 1.18)	1.32 (1.06 to 1.65)§*
Metal allergy†	43 (3)	58 (2)	1.27 (0.84 to 1.91)	1.23 (0.77 to 1.98)	1.54 (0.83 to 2.83)
Respiratory allergy†	154 (11)	271 (9)	1.11 (0.90 to 1.38)	1.15 (0.90 to 1.47)	0.98 (0.69 to 1.39)
Food allergy†	19 (1.4)	40 (1.5)	1.01 (0.58 to 1.76)	1.04 (0.55 to 1.97)	1.04 (0.43 to 2.48)
Plants and pollen†	130 (9)	293 (10)	0.94 (0.75 to 1.18)	0.96 (0.74 to 1.24)	0.91 (0.64 to 1.31)
Allergy to chemicals†	24 (1.8)	51 (1.9)	0.85 (0.51 to 1.40)	0.81 (0.45 to 1.48)	0.82 (0.36 to 1.83)

*Adjusting for age, sex, residential area, body mass index, education and smoking. Bold values are statistically significant (p<0.05).

†Data only available for the first version of questionnaire, 2006 and prior, N=1884 RA cases and N=2146 controls.

‡Interaction term with smoking was significant (p<0.05). OR shown assumes most common scenario (never smoker).

§Interaction term with age was significant (p<0.05). OR shown assumes median age (55 years).

ACPA, anticitrullinated peptide antibodies; EIRA, Epidemiological Investigation of Rheumatoid Arthritis; RA, rheumatoid arthritis.

Table 3 Association of allergic conditions with RF positive RA among the EIRA cases from 1995 to 2016

Allergic condition	N (%) or median (IQR)		
	RF +RA cases (N=2301)	Controls (N=5429)	Adjusted* OR (95% CI) for RF +RA
Animal dander	62 (7)	134 (5)	1.47 (1.06 to 2.03)
Allergic rhinitis	180 (9)	387 (8)	1.35 (0.99 to 1.84)†
Atopic dermatitis	227 (11)	453 (10)	1.04 (0.87 to 1.23)
Metal allergy	28 (3)	58 (2)	1.25 (0.78 to 2.00)
Respiratory allergy	106 (11)	271 (9)	1.18 (0.92 to 1.51)
Food allergy	12 (1.3)	40 (1.5)	1.00 (0.52 to 1.95)
Plants and pollen	90 (10)	293 (10)	1.03 (0.79 to 1.33)
Allergy to chemicals	15 (2)	51 (1.9)	0.83 (0.46 to 1.51)

*Adjusting for age, sex, residential area, body mass index, education and smoking. Bold values are statistically significant ($p < 0.05$).

†Interaction term with smoking was significant ($p < 0.05$). OR shown assumes most common scenario (never smoker).

EIRA, Epidemiological Investigation of Rheumatoid Arthritis; RA, rheumatoid arthritis; RF, rheumatoid factor.

1.65). While atopic dermatitis was not associated with RA risk overall (aOR 1.16, 95% CI 0.98 to 1.25), interaction analyses indicated a statistically significant association with RA for individuals aged 60 years or higher at RA diagnosis (online supplemental table S1). For example, at age 20 years, the aOR for all RA was 0.67 (95% CI 0.46 to 0.98), whereas at age 80 years, the aOR for all RA was 1.71 (95% CI 1.17 to 2.51) and for ACPA-negative RA was aOR 2.33 (95% CI 1.37 to 3.96). Similarly, allergic rhinitis was not associated with RA in smokers (aOR 0.89, 95% CI 0.72 to 1.09), but was associated among never smokers (aOR 1.30, 95% CI 1.00 to 1.68).

The association of allergic diseases with risk of RF-positive RA was nearly identical to that of ACPA-positive RA (table 3). The duration in years that any allergy (combined, overall) occurred before RA did not impact its association with RA (aOR 0.98, 95% CI 0.92 to 1.05). Characteristics of participants missing any of the covariates were similar to those with complete data except that those with missing data had a slightly lower educational level and were more likely to be never smokers (online supplemental table S2).

DISCUSSION

This population-based case-control study of incident RA demonstrated that overall, allergic diseases were not associated with risk of RA. However, we identified animal dander allergy as a novel risk factor for RA, especially ACPA-positive RA. In addition, atopic dermatitis was associated with RA, though this association was confined to ACPA-negative RA and/or older adults. Finally, allergic rhinitis was associated with increased risk of RA in never smokers.

The lack of association between metal, respiratory, plant/pollen and chemical allergies and RA risk is novel to this study. Metal and chemical allergies had never been studied before. Asthma has been associated with increased risk of RA,^{3 4} including in this population,¹⁰ but non-asthma respiratory allergies including cold

and effort asthma had not yet been studied. Two prior studies showed no association between grass allergy and RA,^{3 15} supporting this study's observed lack of association between plant/pollen allergies and RA. The lack of association between food allergy and RA was initially surprising given prior studies suggesting an association.^{3 11-13} However, all of those were cross-sectional studies of prevalent rather than incident RA as done in this study.^{3 11-13} Furthermore, one only asked participants about shellfish and nut allergy,³ one was an animal study using IgE as a proxy for food allergy,¹³ and one was a case series of four patients,¹¹ raising questions about their validity. In addition, another study also showed no association between food allergy and RA.¹⁴ Overall, the lack of association between many allergens and RA can provide reassurance to patients and clinicians.

Our observed association between animal dander allergy and incident RA, especially ACPA-positive RA, was a novel finding to this study. One prior study investigated pet allergy and RA and found no association.³ However, that study found a similar positive direction of association (OR 1.15 in the incident cohort), had only 175 incident RA cases, and did not divide RA patients by ACPA status. Furthermore, horse exposure has recently been associated with increased risk of granulomatosis with polyangiitis.²² The mechanism for such associations between animal exposure and rheumatic disease may involve respiratory irritation, as respiratory diseases have been associated with RA¹⁰ and other rheumatic diseases such as inflammatory myopathies.²³ While this novel finding will require further replication, it represents a potentially modifiable risk factor for individuals at high risk of RA.

We noted a weak association between allergic rhinitis and RA. While many cross-sectional studies of allergic rhinitis and prevalent RA have been performed with mixed results, the two prospective studies of incident RA did show a positive association like this study.^{5 6} The particularly strong association among never smokers is unique to our study. One reason for the negative association

between allergic rhinitis and smoking could be collider stratification bias, where conditioning on a common effect (ie, RA) induces a negative correlation between its risk factors.²⁴ Nevertheless, among the two studies of allergic rhinitis reporting smoking, the one with the lower prevalence of smoking (46%) reported a strong association with RA,²⁵ while the one with a relatively high prevalence of smoking (64%) reported no association.²⁶ Our recent study also showed that respiratory diseases, including chronic upper respiratory diseases such as allergic rhinitis, were associated with increased risk of RA predominately in never smokers.¹⁰

We also found an association between atopic dermatitis and RA for older adults as well as ACPA-negative RA. Historically, several studies showed no association between atopy and RA, but all were small, studied prevalent RA and did not control for confounders.^{14 16 27–30} More recent studies have shown a positive association between atopic diseases and RA.^{3 6 25 31} The association with atopic dermatitis in our study is supported by two other recent studies showing pre-existing atopic dermatitis was associated with incident RA.^{5 32} A third study found a statistically non-significant association with atopic dermatitis, but did find older-aged women with multiple allergic conditions had increased risk of RA.⁶ The association with ACPA-negative RA could indicate misclassification of diseases such as psoriatic arthritis. Nevertheless, the association between atopic dermatitis, age and ACPA-negative RA merits further exploration.

The bidirectional association between certain atopic and autoimmune diseases supports a possible association between atopic diseases and RA that merits further study. For example, in one study, RA was associated with increased risk of developing allergic conditions such as asthma and allergic rhinitis.²⁵ Similarly, autoimmune disease in parents increases risk of allergic disease in children.³³ Shared environmental risk factors like smoking, overlapping genetic risk³⁴ or shared immune dysregulation³⁵ such as cytokine activation³⁶ may all play a role in this bidirectional association. Epithelial barrier disruption via could represent another shared mechanism. Indeed, skin disruption from atopic dermatitis and/or filaggrin mutations increase risk of other allergic diseases such as allergic rhinitis and asthma in a process known as ‘atopic march,’ and could similarly sensitise the immune system to autoimmune diseases.³⁷ Investigating genetic variants and gene by environment interactions in these individuals with both atopic and autoimmune disease may help uncover disease pathogenesis.

This large study benefited from its population-based design, precise incident RA classification, and adjustment for many confounders. However, it has several limitations. First, the epidemiology of allergic conditions may not generalise outside of its geographical area, as allergic diseases vary significantly by geographical area.³⁸ Second, as a case–control study, it may be susceptible to recall bias, artificially increasing the observed associations. Third, the exposures in this study were self-reported and may

therefore be prone to misclassification. We also had no information on childhood-onset versus adult-onset allergies. Fortunately, however, self-reported allergic diseases such as atopic dermatitis have high validity,³⁹ and the prevalence of allergic diseases in this study is similar to published prevalences in the general population.^{38 40 41} Fourth, sample size was too small to study each of the 59 allergic conditions separately, including some specific food allergies of interest such as nuts or eggs. Fifth, residual confounding (eg, asthma) is possible. Finally, multiple hypotheses were tested in this study, though all were based on a prespecified study protocol.

In conclusion, this study of incident RA found that most allergies overall are not associated with RA, but also that several atopic diseases including animal dander allergy, atopic dermatitis, and allergic rhinitis are associated with increased risk of RA.

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Contributors All authors were involved in the drafting and critical review of the manuscript and approved the final version for submission. VK was responsible for overall content as the guarantor. HW, LA, LK, MH and JA were involved in acquisition of the data. VK, HW, MH and JA were involved with the conception or design of the work. VK, HW, CC and MH were involved with the analysis of the data in the manuscript. All authors were involved with the interpretation of data in the manuscript. All authors agreed to be accountable for all aspects of the work and attest to the accuracy and integrity of the work.

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Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and was approved by Karolinska Institutet Ethics Committee approval: (EPN 96-174, 2006/476-31/4, 2007/889-31/2, 2007/1443-32). Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement All data relevant to the study are included in the article or uploaded as online supplemental information.

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