

Association of Asthma with Rheumatoid Arthritis: A Population-Based Case-Control Study



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What is already known about this topic? Asthma is typically considered a chronic inflammatory airway disorder with significant heterogeneity. A link between asthma and risk of other chronic inflammatory diseases is poorly understood.

What does this article add to our knowledge? Because asthma poses a significantly increased risk for rheumatoid arthritis (RA), RA may be an underrecognized asthma-associated comorbidity in a subgroup of patients with asthma. Development of strategies to identify this subgroup of patients with asthma will be warranted.

How does this study impact current management guidelines? Because RA, a potential asthma-associated comorbidity, is relatively underrecognized by caregivers and clinicians, and poses a serious threat to the health of patients with asthma, the guidelines need to address asthma-associated comorbidity including RA to inform and guide clinicians for a timely diagnosis and management of RA.

BACKGROUND: T_H1 and T_H2 cells have counterregulatory relationships. However, the relationship between asthma, a T_H2-predominant condition, and risk of systemic inflammatory diseases such as rheumatoid arthritis (RA), a T_H1 condition, is poorly understood.

OBJECTIVE: We aimed to determine whether asthma was associated with increased risks of incident RA among adults. **METHODS:** We conducted a retrospective population-based case-control study that examined existing incident RA cases and controls matched by age, sex, and registration year from the general population in Olmsted County, Minnesota, between January 2002 and December 2007. We performed comprehensive medical record reviews to ascertain asthma status using predetermined asthma criteria. The frequency of a history of asthma before the index date was compared between cases and controls. Logistic regression models were used to adjust for confounding factors.

RESULTS: We enrolled 221 RA cases and 218 controls. Of the 221 RA cases, 156 (70.6%) were females, 207 (93.7%) were white, the median age at the index date was 52.5 years, and 53 (24.0%) had a history of asthma. Controls had similar characteristics except that 35 of 218 controls (16.1%) had a history of asthma. After adjustment for sex, age, smoking, body mass index, socioeconomic status, and comorbidity, asthma was significantly associated with increased risks of RA (adjusted odds ratio, 1.74; 95% CI, 1.05-2.90; *P* = .03).

CONCLUSIONS: Despite the counterregulatory relationship between T_H1 and T_H2 cells, patients with asthma had a significantly higher risk of developing RA than healthy individuals. © 2017 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2018;6:219-26)

Key words: Asthma; Rheumatoid arthritis; Risk; Adults; Epidemiology

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Rheumatoid arthritis (RA) is an autoimmune disease characterized by synovial inflammation and hyperplasia, autoantibody formation (ie, rheumatoid factor and anti-citrullinated protein antibody), and destruction of joint cartilage and bone.¹ RA develops as the result of a complex interplay among susceptibility genes (ie, HLA-DRB1 locus), environmental triggers (ie,

Abbreviations used

aOR- Adjusted odds ratio
 HOUSES- HOUSing-based index of SocioEconomic Status
 MIC- Major histocompatibility complex
 NK- Natural killer
 OR- Odds ratio
 NKG2D- Natural killer group 2D
 RA- Rheumatoid arthritis
 REP- Rochester Epidemiology Project

smoking and socioeconomic status), and epigenetic modification, which promote loss of tolerance to self-proteins containing a citrulline residue, which is produced by posttranslational alteration.¹ RA is considered a T_H1 disorder, as reported in experimental,² clinical,³ and epidemiological studies.⁴ For instance, an *in vitro* study demonstrated that T-cell clones from the synovium of patients with RA produced large amounts of IFN- γ , with dominant T_H1/T_H0 patterns.²

Atopic diseases such as asthma are considered a T_H2-predominant disease.⁵ Asthma is a chronic inflammatory disorder of the airways with significant heterogeneity.⁶ A recent review argues that the impact of asthma goes beyond the airways, suggesting that asthma may not be a mere airway disease, but a chronic disease causing systemic inflammatory dysfunctions.⁷ Modena et al⁸ characterized bronchial airway epithelial cell gene expression (genetic clusters) and phenotypes (subject clusters) of 155 patients with severe asthma and determined that although a subgroup of patients with asthma showed expected T_H2-high immune profiles, another subgroup demonstrated a gene expression of T_H1-predominant inflammatory pathway such as TNF- α . These data suggest that significant phenotypic heterogeneity of asthma can be correlated with genetic clusters underlying molecular pathways including coexisting T_H2 and T_H1 immune pathways or endotypes. Therefore, a subgroup of asthma may exhibit systemic inflammatory features and its associated molecular pathway gearing toward T_H1 immune responses (eg, TNF- α). Hence, it is worthwhile to determine whether there is an association between asthma and the risk of T_H1-predominant conditions such as RA and to characterize a subgroup of patients with asthma at an increased risk of developing RA.

Although several studies assessed relationships between asthma and the risk of RA, the results have been inconsistent primarily due to non-hypothesis-driven analysis, sampling bias, and/or measurement bias. Moreover, no population-based study has tested *a priori* the hypothesis that asthma is associated with an increased risk of RA using both predetermined criteria for asthma status and RA.

Delineating the relationship between asthma and the risk of RA has clinical and scientific significance because asthma affects a significant proportion of individuals worldwide. Thus, it may provide important scientific insights into relatively unexplored systemic effects of asthma on serious chronic inflammatory diseases such as RA as well as the effect of coexistent RA on asthma course and management.

To address the aforementioned question, we conducted a population-based case-control study using specific predetermined criteria for both asthma and RA. We hypothesized that asthma increases the risk of RA.

METHODS**Study setting**

All subjects were residents of Olmsted County, Minnesota, which is located in southeastern Minnesota.⁹ The Olmsted County population is similar to the US white population, with the exception of a higher proportion of the working population employed in the health care industry.¹⁰ Medical records-based research using the geographically defined population of Olmsted County is possible through the Rochester Epidemiology Project (REP).⁹ The REP record-linkage system links all inpatient and outpatient medical records, from the Mayo Clinic, the Olmsted Medical Center, and their affiliated hospitals, as well as private practitioners and other health care providers in Olmsted County.

Study design and subjects

This is a population-based, retrospective case-control study that used an existing population-based cohort of incident adult RA cases between January 1, 2002, and December 31, 2007, in Olmsted County, Minnesota.¹¹ Briefly, the original study included 237 incident RA cases who fulfilled the 1987 American College of Rheumatology classification criteria.¹² It also included 237 control subjects (1:1 matching) who had no history of RA matched to each case by sex, birth ($\pm$ 3 years), and registration year and were randomly selected from the same source population using the REP medical records linkage system. Because the detection of asthma is a function of follow-up duration, we addressed this concern by matching cases and controls by registration and index years, resulting in a similar follow-up duration. The exclusion criteria for cases and controls were change of research authorization, insufficient medical records, and medical conditions making it difficult to ascertain asthma status (Table I). The study was approved by the institutional review boards of both Mayo Clinic and Olmsted Medical Center.

Exposure ascertainment (asthma status)

For determining a history of asthma, we conducted comprehensive medical record reviews to apply predetermined asthma criteria (Table I), which have been extensively used in research¹⁰ and were found to have excellent construct validity and reliability.¹³ We included both definite and probable asthma because most probable patients with asthma become definite over time.¹⁰ We also obtained asthma status based on symptoms, health care services, and treatments within 1 year before the index date. *Active asthma (current asthma)* at the index date was defined as the occurrence of any asthma-related episodes including asthma symptoms (ie, cough with wheezing, shortness of breath, and chest tightness), asthma medications, or unscheduled office visits, emergency department visits, urgent care visits, or hospitalization for asthma within 1 year before the index date. *Inactive asthma* was defined as the absence of aforementioned asthma-related events within 1 year before the index date. To assess the impact of asthma medications on RA risk, we collected information on asthma medication use including inhaled and oral corticosteroids within 3 months of the index date.

Other variables

Demographic and clinical characteristics included sex, age, race, family history of asthma, and other atopic conditions. Atopy status defined by aero- or food allergen was collected through comprehensive review of medical charts and the REP. We collected data on other atopic conditions such as allergic rhinitis, atopic dermatitis, and food allergy on the basis of a physician diagnosis documented in medical records to examine whether coexistence of allergic diseases

TABLE I. Definition of asthma

Patients were considered to have *definite* asthma if a physician made a diagnosis of asthma and/or if each of the following 3 conditions was present, and they were considered to have *probable* asthma if only the first 2 of the following 3 conditions were present:

1. history of cough with wheezing and/or dyspnea *or* history of cough and/or dyspnea plus wheezing on examination;
2. substantial variability in symptoms from time to time or periods of weeks or more when symptoms were absent; and
3. 2 or more of the following:
 - sleep disturbance caused by nocturnal cough and wheeze,
 - nonsmoker,
 - nasal polyps,
 - blood eosinophilia $>300/\mu\text{L}$,
 - positive wheal-and-flare skin test result *or* increased serum IgE level,
 - history of hay fever or infantile eczema *or* cough, dyspnea, and wheezing regularly on exposure to antigen,
 - pulmonary function tests showing 1 FEV₁ or FVC value of $<70\%$ of predicted value and another with $\geq 20\%$ improvement to an FEV₁ of $>70\%$ of predicted value *or* a methacholine challenge test showing $\geq 20\%$ decrease in FEV₁, and
 - favorable clinical response to bronchodilator.

Patients were excluded from the study if any of these conditions was present:

- pulmonary function tests that showed FEV₁ to be consistently $<50\%$ of predicted value or diminished diffusion capacity;
- tracheobronchial foreign body at or about the incidence date;
- hypogammaglobulinemia (IgG <2.0 mg/mL) or other immunodeficiency disorder;
- wheezing occurring only in response to anesthesia or medications;
- bullous emphysema or pulmonary fibrosis on chest radiograph;
- PiZZ α_1 -antitrypsin;
- cystic fibrosis;
- other major chest disease, such as juvenile kyphoscoliosis or bronchiectasis.

FVC, Forced vital capacity.

with asthma further increased the risk of RA compared with asthma alone. We applied an individual housing-based socioeconomic status measure we developed and validated (termed housing-based index of socioeconomic status [HOUSES]) to our cohort, which previously showed associations with the risk of RA.¹⁴ The presence of comorbid conditions was assessed using the Charlson comorbidity index without including asthma and RA, which was included in a previous study.¹⁴ We reviewed each individual's medical charts to determine differences in health care accessibility between groups by examining the administration of influenza vaccine in the index year or the preceding year and of pneumococcal vaccine ever before the index date.

Statistical analysis

Baseline characteristics were summarized using count (percentages) for categorical variables and median (interquartile range) for continuous variables, and were tested for an association with RA in univariate models using unconditional logistic regression controlling for matching factors because some pairs in the original study cohort were broken after excluding subjects according to the exclusion criteria. We fit multivariable models adjusting for pertinent variables based on known risk factors for RA.¹⁵⁻¹⁷ In addition, subgroup analyses such as active versus inactive asthma, sex, and age were conducted to examine the effect of clinical parameters on the risk of RA. All statistical analyses were performed using SAS software, version 9.3 (SAS Institute Inc, Cary, NC). All statistical tests were 2-sided, with a *P* value of less than .05 indicating statistical significance.

RESULTS

Study subjects

A total of 221 cases and 218 controls were included after excluding 35 subjects causing imbalance between groups. The reasons for exclusion were no research authorization (*n* = 23, change from the original study), insufficient medical records to

determine asthma (*n* = 1), bullous emphysema or pulmonary fibrosis on chest x-ray (*n* = 4), kyphoscoliosis or bronchiectasis (*n* = 6), and hyper-IgA syndrome (*n* = 1).

The sociodemographic characteristics of the subjects are summarized in Table II. Overall, cases and controls were similar except for the HOUSES in quartiles. Among 221 cases, 156 (70.6%) were female, 207 (93.7%) white, and the median age (interquartile range) at the index date was 52.5 years (41.7-65.7). The HOUSES was significantly lower among RA cases than among controls (*P* = .01).

Comparison of clinical characteristics between RA cases and controls

Of the 221 cases, 53 (24.0%) had asthma defined by pre-determined criteria, whereas 35 (16.1%) of 218 controls had asthma (odds ratio [OR], 1.68; 95% CI, 1.04-2.71; *P* = .03; Table II). Although asthma as a whole tended to be associated with the risk of RA, the proportion of active or inactive asthma among patients with asthma did not differ between groups (*P* = .74). Among patients with asthma, those with other atopic conditions tended to have a higher risk of RA compared with those without (OR [95% CI], 1.91 [1.08-3.37] vs 1.29 [0.60-2.82]). Patients with RA were more likely to have RA compared with controls (31.2% vs 22.0%; OR, 1.61; 95% CI, 1.05-2.48; *P* = .03), but no significant difference was observed for atopic dermatitis (*P* = .61) or food allergy (*P* = .16). Family history of asthma, other atopic conditions, or having either did not show any difference between groups. Chronic obstructive pulmonary disease was not associated with the risk of RA (*P* = .82). Patients with RA were more likely to have hypertension compared with controls (OR, 1.89; 95% CI, 1.22-2.93; *P* = .004). No difference was observed in body mass index (*P* = .69), our modified Charlson comorbidity index categories, which removed chronic obstructive pulmonary disease- and RA-related conditions as a measure for comorbidity (*P* = .54), or

TABLE II. Sociodemographic and clinical characteristics of the study subjects and their associations with the risk of RA in univariable analysis

Characteristic	RA case (n = 221)	Controls (n = 218)	OR* (95% CI)	P value
Sociodemographic variables				
Female sex, n (%)	156 (70.6)	154 (70.6)		.99
Age at index date (y), median (IQR)	52.5 (41.7-65.7)	54.2 (42.6-66.7)		.52
White, n (%)	207 (93.7)	205 (94.0)	0.96 (0.44-2.10)	.91
HOUSES in quartiles, n (%)				.01
Quartile 1 (lowest SES)	63 (29.3)	43 (20.6)	1.00 (reference)	
Quartile 2	60 (27.9)	46 (22.0)	0.87 (0.50-1.51)	
Quartile 3	47 (21.9)	59 (28.2)	0.52 (0.30-0.90)	
Quartile 4 (highest SES)	45 (20.9)	61 (29.2)	0.48 (0.28-0.84)	
Education level, n (%)				.09
<High school	18 (8.4)	19 (8.8)	1.00 (reference)	
High school	57 (26.6)	56 (26.0)	0.49 (0.20-1.21)	
Technical school/college	124 (57.9)	109 (50.7)	1.17 (0.58-2.38)	
Graduate school	15 (7.0)	31 (14.4)	1.06 (0.50-2.23)	
Smoking status at index date, n (%)				.78
Never	118 (53.4)	121 (55.5)	1.00 (reference)	
Current	34 (15.4)	34 (15.6)	1.00 (0.58-1.73)	
Former	69 (31.2)	63 (28.9)	1.16 (0.75-1.81)	
Asthma-related variables, n (%)				
Asthma by PAC†	53 (24.0)	35 (16.1)	1.68 (1.04-2.71)	.03
Asthma by physician diagnosis	51 (23.1)	32 (14.7)	1.77 (1.09-2.90)	.02
Asthma status at index date				.09
No asthma	168 (76.0)	183 (83.9)	1.00 (reference)	
Inactive asthma	24 (10.9)	17 (7.8)	1.56 (0.81-3.01)	
Active asthma	29 (13.1)	18 (8.3)	1.80 (0.96-3.38)	
Asthma and atopic conditions				.07
No asthma	168 (76.0)	183 (83.9)	1.00 (reference)	
Asthma without other atopic conditions	15 (6.8)	13 (6.0)	1.29 (0.60-2.82)	
Asthma with other atopic conditions	38 (17.2)	22 (10.1)	1.91 (1.08-3.37)	
Other atopic conditions, n (%)				
Allergic rhinitis	69 (31.2)	48 (22.0)	1.61 (1.05-2.48)	.03
Atopic dermatitis	31 (14.0)	27 (12.4)	1.15 (0.66-2.01)	.61
Food allergy	6 (2.7)	2 (0.9)	3.15 (0.63-15.9)	.16
Family history of asthma	24 (10.9)	26 (11.9)	0.87 (0.48-1.59)	.65
Family history of atopic conditions	7 (3.2)	4 (1.8)	1.69 (0.48-5.95)	.41
Family history of asthma or atopic conditions	25 (11.3)	28 (12.8)	0.84 (0.47-1.50)	.55
Atopy status defined as aeroallergen or food	16 (7.2)	16 (7.3)	0.66 (0.10-4.54)	.91
Comorbid conditions,‡ n (%)				
Chronic obstructive pulmonary disease	39 (17.6)	41 (18.8)	0.62 (0.32-1.23)	.82
Diabetes mellitus	28 (12.7)	25 (11.5)	1.15 (0.64-2.05)	.64
Coronary heart disease	17 (7.7)	26 (11.9)	0.95 (0.58-1.54)	.17
Congestive heart failure	5 (2.3)	7 (3.2)	1.35 (0.89-2.05)	.61
Alcoholism	16 (7.2)	13 (6.0)	1.23 (0.57-2.63)	.60
Hypertension	144 (65.2)	119 (54.6)	1.89 (1.22-2.93)	.004
Dyslipidemia	142 (64.3)	129 (59.2)	0.74 (0.23-2.40)	.15
Body mass index				.69
Underweight	2 (0.9)	3 (1.4)	0.80 (0.13-5.06)	
Normal	62 (28.1)	68 (31.2)	1.00 (reference)	
Overweight	67 (30.3)	56 (25.7)	1.33 (0.81-2.20)	
Obese	90 (40.7)	91 (41.7)	1.10 (0.70-1.72)	
Charlson comorbidity index categories				.54
0	104 (47.1)	110 (50.5)	1.00 (reference)	
1-2	84 (38.0)	73 (33.5)	1.27 (0.83-1.94)	
≥3	33 (14.9)	35 (16.1)	1.08 (0.60-1.94)	

(continued)

TABLE II. (Continued)

Characteristic	RA case (n = 221)	Controls (n = 218)	OR* (95% CI)	P value
Inhaled corticosteroid treatment at index date,§ n (%)				.66
No	37 (69.8)	26 (74.3)	1.00 (reference)	
Yes	16 (30.2)	9 (25.7)	1.25 (0.47-3.28)	
Burst course of systemic steroid at index date,§ n (%)				.98
No	53 (100.0)	34 (97.1)	1.00 (reference)	
Yes	0 (0.0)	1 (2.9)		
Influenza vaccine, n (%)	118 (53.4)	101 (46.3)	1.37 (0.93-2.01)	.11
PPV23 vaccine, n (%)	67 (30.3)	55 (25.2)	1.60 (0.97-2.64)	.06

IQR, Interquartile range; PAC, predetermined asthma criteria; SES, socioeconomic status.

*ORs and P values are from logistic regression predicting RA cases adjusted for sex and age.

†PAC (Table I).

‡Comorbid conditions are not mutually exclusive because some subjects had multiple comorbid conditions.

§The results were analyzed by using a subgroup of subjects with asthma by PAC.

TABLE III. The association between asthma by PAC and the risk of RA in multivariable analysis*

Variables	aOR	95% CI	P value
Asthma by PAC	1.73	1.03 2.92	.04
Female sex	1.09	0.69 1.71	.73
Age (y)	0.98	0.97 1.00	.04
Body mass index (kg/m ²)			.539
Underweight <18.5	0.60	0.09 4.01	
Normal ≥18.5-24.9	1.00	Reference	
Overweight ≥25-29.9	1.14	0.67 2.00	
Obese ≥30	0.80	0.48 1.33	
HOUSES in quartiles			.03
Quartile 1 (lowest SES)	1.00	Reference	
Quartile 2	0.81	0.46 1.43	
Quartile 3	0.53	0.30 0.95	
Quartile 4 (highest SES)	0.45	0.25 0.81	
Smoking status at index date			.66
Never	1.00	Reference	
Former	1.06	0.66 1.70	
Current	0.78	0.43 1.43	
Hypertension	1.83	1.12 3.00	.02
Coronary heart disease	0.46	0.22 0.95	.04
Dyslipidemia	1.33	0.84 2.12	.23

PAC, Predetermined asthma criteria; SES, socioeconomic status.

*Adjusted for sex, age, body mass index, HOUSES (quartiles), smoking status, hypertension, coronary heart disease, dyslipidemia, and asthma status by PAC.

vaccines (ie, influenza and pneumococcus) between groups. All asthma medications, including inhaled (OR, 1.25; 95% CI, 0.47-3.28; $P = .66$) or systemic corticosteroids ($P = .98$) at the time of the index date, were not associated with the risk of RA among patients with asthma.

Association of asthma with risk of RA

Table III presents the association between asthma and the risk of RA in a multivariable analysis. After adjustment for the known potential confounders for RA including sex, age, body mass index, smoking status, socioeconomic status as measured by HOUSES (quartiles), hypertension, coronary heart disease, and dyslipidemia, the association between asthma by predetermined criteria and RA remained significant (adjusted OR [aOR], 1.73;

95% CI, 1.03-2.92; $P = .04$). After adjusting for the aforementioned confounders, both inactive (aOR, 1.58; 95% CI, 0.77-3.16) and active asthma (aOR, 1.91; 95% CI, 0.96-3.80) at the index date tended to be associated with an increased risk of incident RA compared with no asthma, but it did not reach statistical significance ($P = .11$, data not shown).

Association of other factors with the risk of RA

In separate models that controlled for the aforementioned adjusting covariates in Table III, the association between allergic rhinitis and RA remained significant (aOR, 1.74; 95% CI, 1.09-2.78; $P = .02$, data not shown). Allergic rhinitis, although showing a significant difference between groups in the univariate analysis, was not included in the multivariable analysis given its strong collinearity with asthma. Subgroup analyses with regard to sex and age showed no significant interaction effect on the association of asthma with RA (data not shown).

DISCUSSION

This population-based study in adults suggests that asthma is associated with an increased risk of RA. This may also be true for other atopic conditions, such as AR. Asthma medications or other comorbid conditions such as chronic obstructive pulmonary disease did not account for this association because they were not associated with the risk of RA.

Our study results are consistent with a previous study showing the female predominance of RA epidemiology (71%).¹ We found a previously reported association between RA and hypertension, although the reason was unknown.¹⁸ We believe our results are unlikely due to covariate imbalance (ie, susceptibility bias) because we controlled for all potential and known RA risk factors. In fact, in contrast to our anticipation (ie, frequent use of systemic corticosteroids in patients with asthma might mask clinical manifestations of RA and, therefore, delay or lower the likelihood of detecting RA), our results showed that asthma significantly increased the risk of RA. Also, because our asthma criteria were specific and abstractors were blinded for case and control status, observation bias (performance bias) is unlikely. Because the detection of asthma is a function of follow-up duration, we addressed this concern by designing the present study in a way that cases and controls were matched according to their registration and index dates; thus, they had similar observation periods. Given the serious clinical manifestations of RA,

asthma is unlikely to result in differential detection of RA between patients with and without asthma. In addition, we examined differential health care accessibility between groups by examining influenza and pneumococcal vaccinations and did not find significant differences between groups. Therefore, detection bias is unlikely to account for the association between asthma and the risk of RA. Apart from asthma, allergic rhinitis was associated with an increased risk of RA, which is consistent with a recent report showing that patients with allergic rhinitis had a higher risk of developing RA (hazard ratio, 1.48; 95% CI, 1.20–1.79) in cohorts of 170,570 with and 170,238 without allergic diseases.¹⁹ This may explain our finding of a higher risk of RA among patients with asthma with other atopic conditions compared with those without, and potentially suggest their biological coherence. Taken together, our results suggest that asthma is independently associated with an increased risk of RA.

There are 2 cohort studies showing positive associations of asthma with the risk of RA. Lai et al¹⁹ demonstrated, by using a nationwide population-based database in Taiwan, that patients with asthma had a significantly increased risk of RA. Another nationwide cohort study conducted in Sweden using 148,295 hospitalized patients with asthma found that patients with asthma were more likely to develop RA than the general population.²⁰ Two case-control studies^{21,22} also corroborated the positive associations between asthma and RA. Of note, a case-control study looking at 100 patients with RA and 50 controls reported that a significantly higher number of patients with RA had a history of wheeze compared with controls (18% vs 4%, $P < .05$), that all lung function measures were significantly lower in the RA group, and that a significantly higher number of patients with RA exhibited bronchial reactivity to inhaled methacholine (55% vs 16%, $P < .05$), thereby providing objective evidence that patients with RA may have decreased lung function.²² Another nationwide cohort study performed in Finland²³ and 2 cross-sectional studies^{24,25} showed the coexistence of asthma and RA although its temporal direction is unclear (ie, whether asthma preceded RA or vice versa). Although these results are consistent with ours, they are limited in that they used a self-reported diagnosis of asthma^{21,24,25} or *International Classification of Diseases, Ninth Revision* codes for asthma,^{19,20,23} included only women,²¹ had small incidence cases,²¹ did not have controls,²⁰ or did not fully control for potential confounders such as socioeconomic status, smoking status, and body mass index.^{19,20,23–25} In addition to the positive association between asthma and RA, there are previous studies suggesting the coexistence of asthma and other T_H1 diseases, namely, coronary heart disease,^{26,27} celiac disease,^{20,23,28} and diabetes mellitus.^{23,25,29,30}

On the contrary, some articles suggest that there are inverse or no associations between asthma and the risk of RA; however, these studies had significant methodological limitations: a cross-sectional design,^{31,32} a small sample size,^{31,33,34} or only young (unsuitable) study subjects,^{29,35} convenience samples for cases and controls,^{33,36} unclear sampling frame^{34,37} or unclear case definition,³⁴ a self-reported asthma and/or RA ascertainment,^{31–34,36–38} a short observation period,²³ detection bias,³² or potential covariate imbalance,³⁴ or inadequate adjustments.³⁴ For example, Tirosh et al³⁵ followed 488,841 subjects of the Israeli Defense Force database during their military service period of 36 and 22 months for men and women, respectively, and suggested that the prevalence of RA was lower in women with asthma when compared with those without; however, their subjects were young

adults (18–21 years) and hence, not in the susceptible age for RA. Thus, their subjects were unsuitable to determine the relationship between asthma and the risk of RA.

There may be a few congruent immunogenetic mechanisms underlying the association between asthma and the risk of RA. There may be genetic mechanisms shared by asthma and RA, such as HLA-DRB1,³⁹ TNF- α ,⁸ and a genetic interaction between CD86 and CD40L.⁴⁰ Another potential mechanism is the role of natural killer (NK) group 2D (NKG2D) expressed by NK cells. It is an activating receptor expressed on mature NK cells, NK T cells, and subsets of $\gamma\delta$ and $\alpha\beta$ T cells,^{41,42} is known to mediate the “stress surveillance” function of NK cells, and recognizes ligands from MHC class I chain-related molecules (major histocompatibility complex [MIC] A or MICB) and UL16-binding proteins in man, which are upregulated following DNA damage and on transformed cells.^{43,44} A study investigated the role of NKG2D and NK-cell effector functions by using house dust mite–triggered asthma mouse models and demonstrated that allergic inflammation was markedly reduced after house dust mite allergen exposures in NKG2D-deficient mice, but was reestablished by adoptive transfer of wild-type NK cells⁴⁵; they concluded that NK-cell–intrinsic expression of NKG2D is required for allergic pulmonary inflammation in response to house dust mite allergen.⁴⁵ Regarding RA, a significant proportion of CD4⁺CD28[−] T cells from patients with RA were reported to express NKG2D, which stimulated autoreactive responses against RA synoviocytes demonstrating abnormal expression of the NKG2D ligands MICA or MICB, resulting in dysregulated autoinflammatory responses.⁴⁶ Thus, we postulate that in a subset of patients with asthma, enhanced NKG2D activity in immune cells may contribute toward the generation of autoimmunity that facilitates the development of RA. Last, studies have suggested increased IL-17A and IL-17F activities in the airways of patients with asthma⁴⁷ and in synovial fluids of patients with RAHH,⁴⁸ and that T_H17 cells from patients with RA can induce chronic destructive disorder and inflammation.⁴⁹ Therefore, T_H17 cells may be a mediator linking asthma to RA. Because our study results indicate that a subgroup of patients with asthma is at an increased risk of RA, characterizing subgroups of individuals with asthma with regard to the risk of RA by using immunogenetic and clinical factors is warranted.

Clinicians and patients should be aware that a history of asthma may be an underrecognized risk factor for RA in adults. An important clinical finding worth mentioning is that asthma-related medications did not have a significant effect on the risk of RA. Therefore, clinicians and patients with asthma need to make an effort to optimally control asthma by using preventive and therapeutic medications.

The main strength of our study is a population-based study design minimizing sampling bias. In addition, this study was based on prospectively identified incident RA cases in Olmsted County, Minnesota, where medical care is virtually self-contained within the community and the REP provides information on individuals attending almost all health care facilities in the county,⁹ which therefore enabled us to track all their medical records throughout their lifetime. Another important strength is the use of predetermined criteria for asthma¹⁰ and the 1987 American College of Rheumatology classification criteria for RA.¹² However, our study has inherent limitations as a retrospective study. Although incident RA cases were identified retrospectively, silent patients with RA might have been missed

in our study. We suspect that patients with asthma who have been on corticosteroids might have overrepresented these sub-clinical RA cases who might have been missed in our study. If this is true, the effect size for the association between asthma and the risk of RA might have been underestimated. The current study has limited data on allergic sensitization. The observation that asthma with other atopic conditions had a stronger association with an increased risk of RA compared with those without may suggest that atopic asthma (vs nonatopic asthma) may drive the observed association. Future studies with sufficient sensitization data are needed to better understand the role of “atopy” in the observed association of asthma with the risk of RA. In addition, the present study is underpowered in fully addressing the heterogeneity of asthma by multiple subgroups as shown in Table II. The subjects were predominantly white; therefore, one should be cautious when generalizing the present findings to other ethnic groups or study settings. The presence of asthma in the controls was relatively high (16.1%) compared with the US nationwide prevalence of 8.4% based on self-reported diagnosis,⁵⁰ but comparable with 15.3% (114 of 742) among the control subjects of another case-control study by our group using the same source population (ie, the REP) and the same asthma criteria and ascertainment process (ie, manual chart review for the predetermined asthma criteria).⁵¹ The discrepancy between our data and the national data may be attributed to the fact that we reviewed the whole available medical record of the subjects (from birth) to the index date irrespective of the current asthma status. Therefore, the incidence of asthma in the cases and controls might be relatively higher than the nationwide prevalence based on self-reported diagnosis, in which case the subjects may not recall a history of their childhood asthma.

In summary, despite the counterregulatory relationship between T_H1 and T_H2 cells, asthma is an underrecognized risk factor for RA. Clinicians should be aware of this association for a timely diagnosis and treatment for RA. Because asthma might have systemic inflammatory features in subgroups of patients and affect a significant proportion of individuals, future research needs to focus on the development of strategies to identify this subgroup of patients with asthma and to delineate the underlying mechanisms.

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