

Investigating Asthma, Allergic Disease, Passive Smoke Exposure, and Risk of Rheumatoid Arthritis

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Objective. Rheumatoid arthritis (RA) is postulated to originate at mucosal surfaces, particularly the airway mucosa. To investigate this hypothesis, we determined the association between RA and asthma, passive smoke exposure, and age at start of smoking.

Methods. For this case-control study, we identified 1,023 cases of RA (175 incident) within a single-center biobank population, using a rules-based algorithm that combined self-report with 2 diagnostic codes. Exposures were self-reported on biobank questionnaires. Logistic regression models were used to calculate the association of exposures with RA, adjusting for potential confounders. Odds ratios (ORs) with 95% confidence intervals (95% CIs) were calculated.

Results. After adjustment for allergies, urban environment, and passive smoke exposure, asthma was found to be associated with RA in the full cohort (OR 1.28 [95% CI 1.04–1.58; $P = 0.02$]) but not the incident RA cohort (OR 1.17 [95% CI 0.66–2.06; $P = 0.60$]). History of allergic disease was associated with RA in both the full cohort (OR 1.30 [95% CI 1.12–1.51; $P < 0.001$]) and the incident RA cohort (OR 1.61 [95% CI 1.11–2.33; $P = 0.01$]), especially food allergy, which was significantly associated with RA in the full cohort (OR 1.38 [95% CI 1.08–1.75; $P = 0.01$]) and showed a trend toward significance in the incident RA cohort (OR 1.83 [95% CI 0.97–3.45; $P = 0.06$]). Passive smoke exposure at home or work was not associated with RA. Finally, age at start of smoking was not associated with increased odds of developing RA in either the full cohort (OR 1.03 [95% CI 1.00–1.06; $P = 0.03$]) or the incident RA cohort (OR 1.00 [95% CI 0.92–1.08; $P = 0.98$]).

Conclusion. Asthma and allergies may be associated with increased risk of RA. Passive smoke exposure and early age at start of smoking do not appear to influence risk of RA.

INTRODUCTION

Rheumatoid arthritis (RA) is one of the most common autoimmune diseases, affecting nearly 1 in 100 individuals (1). Seropositive RA in particular is hypothesized to originate from inflammation in the respiratory tract, resulting in autoantibody formation that later leads to disease (2,3). However, several questions about this hypothesis of disease generation remain, which, if answered, may help elucidate disease pathogenesis.

First, several studies have shown an association between asthma and RA, which may be explained by a shared immunologic mechanism (4–8). However, a major limitation of these previous studies is the lack of adjustment for allergic disease. Moreover, none included adjustment for secondhand cigarette smoke or urban pollution, which are known contributors to RA (9–12)

and asthma (13,14). It is unclear whether asthma is associated with RA after adjustment for these important confounders.

Second, the association between personal smoking and RA has been well-established (15,16), yet only 3 studies have investigated the association between passive smoke exposure and RA (10,17,18). The results of these studies conflict, with 2 suggesting an association between passive smoking and RA and the other showing no association. None of these prior reports characterized workplace smoke exposure alone or contained information about both the duration and intensity to allow a dose-response analysis. Earlier age of smoking may also be important, but has not yet been studied in patients with RA (19).

Our goal in this study was to clarify these gaps in knowledge related to the oral-respiratory factors that may mediate RA pathogenesis. Specifically, we aimed to determine the association

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of RA with asthma after controlling for allergic disease, urban environment, passive smoke (exposure at home and work), and age at start of smoking. We hypothesized that the association with asthma would be attenuated after adjustment for allergy and environmental pollutants, that passive smoke at higher doses would be associated with RA, and that earlier age at start of smoking would be associated with an increased risk of RA.

PATIENTS AND METHODS

Study design. This case-control study was performed according to the Strengthening the Reporting of Observational studies in Epidemiology (STROBE) guidelines for observational studies (20). The study was approved by the Mayo Clinic and Olmsted County Institutional Review Boards (approval nos. 17-010806 and 060-OMC-17), and was in compliance with the Declaration of Helsinki.

Questionnaire data for this study came from the Mayo Clinic Biobank repository (21). Active recruitment took place from April 2009 to December 2015 in both Minnesota and Florida. Eligibility criteria included age of 18 years or older, ability to communicate in English, capacity to consent, and residence in the US. Approximately 29% of those invited agreed to participate and completed a baseline questionnaire, yielding the 55,898 current participants. Of those, 77% completed the follow-up questionnaire sent ~4 years later. To ensure the validity and quality of data, all questionnaires were visually examined for errors and omissions. Those with >10 errors were returned to participants for correction. A computer program was also used to find logical errors and incorrect skip patterns, flagging records for manual verification. Of the 55,898 biobank participants, ~87% were recruited from primary care locations, including internal medicine, preventive medicine, family medicine, and obstetrics/gynecology. Most of the remaining participants were recruited from orthopedics.

Study population. In this study, we defined cases of RA using a rules-based algorithm that combined self-reported RA on either the baseline or follow-up questionnaire with at least 2 RA diagnostic codes (714.0 or 714.9) 30 days apart. We excluded 38 individuals who reported RA on the baseline questionnaire but not on the follow-up questionnaire, as those individuals are likely to have misrepresented RA status. Using a separate cohort of 732 individuals screened for inclusion in the RA cohort of the Rochester Epidemiology Project (1), which used the 1987 American College of Rheumatology classification criteria for RA (22), we found the positive predictive value (PPV) of this definition to be 88%. This accuracy was superior to that obtained using diagnostic codes alone, which is a widely accepted method.

We also included 78 participants who did not self-report RA but had 3 or more diagnostic codes for RA, with the first code occurring at least 90 days after the most recent survey (presumed incident RA). The incident RA group also included 97 individuals

who self-reported RA on the follow-up questionnaire but not the baseline questionnaire, for a total of 175 incident cases.

To determine the accuracy of our RA definition in the full cohort, we performed manual chart verification using the 2010 ACR criteria in a subset of 100 randomly selected RA cases (23). One of the authors (VLK) performed the main chart review, and another author (JMD) adjudicated any cases with uncertainty. Of the 100 patients selected, 87 were found to have RA or seronegative inflammatory arthritis consistent with RA, for a PPV of 87% (Supplementary Table 1, available on *Arthritis & Rheumatology* web site at <http://onlinelibrary.wiley.com/doi/10.1002/art.40858/abstract>).

We defined the index date as the date of RA diagnosis. The date of RA diagnosis came from the earliest diagnostic code for RA, provided this date was in the age range of RA diagnosis reported by the patient (≤ 19 , 20–49, 50–64, 65–79, or 80+ years), or earlier. If the first diagnostic code occurred after the patient-reported date of RA diagnosis, then we used the patient-reported date of RA diagnosis.

Controls for this study included biobank participants without self-reported RA and no diagnostic codes for RA to ensure none had RA (negative predictive value >99%). We used 3:1 matching for the remaining biobank participants, with matching criteria consisting of recruitment year (within 5 years), recruitment location (Minnesota or Florida), distance from recruitment location (within 500 miles), age at baseline survey (within 5 years), and sex. The index date for each control was defined as the date of RA diagnosis for the corresponding case.

Measures. The prespecified primary exposures of interest included self-reported asthma, presence of passive smoke exposure at home and work, and age at start of smoking regularly. For passive smoke exposure, we also studied the age the smoke exposure started, years of exposure before index date, packs per day, and pack-years before index date. Home and workplace smoke exposure in packs per day was only available in the second version of the baseline questionnaire. Self-report is the most accurate way to study smoking history, and studies suggest that self-reported asthma has a high PPV as well (24,25). We performed a manual verification of self-reported asthma on a random subset of 50 study participants. We used previously published criteria to identify “definite” asthma as a physician diagnosis of asthma during a clinical visit in the chart and/or the presence of each of the following 3 conditions: 1) history of cough with wheezing or dyspnea, 2) variability in symptoms, and 3) ≥ 2 features supportive of the diagnosis, including sleep disturbance, nonsmoker, nasal polyps, blood eosinophilia, elevated IgE level, history of wheezing on exposure to antigen, pulmonary function test results indicative of asthma, and/or favorable clinical response to bronchodilator (26). We defined “probable” asthma as having the first 2 conditions but not the third. Using these criteria, we found 82% of these 50 participants with self-reported asthma to have definite asthma and 8% to have probable asthma (Supplementary Table 2, <http://onlinelibrary.wiley.com/doi/10.1002/art.40858/abstract>).

Table 1. Characteristics of the RA cases and controls at index date of diagnosis*

	RA cases (n = 1,023)	Incident RA subset (n = 175)	Controls (n = 3,061)
Age, mean $\pm$ SD years	50 $\pm$ 16	63 $\pm$ 14	50 $\pm$ 16
Female sex, no. (%)	741 (72)	119 (68)	2215 (72)
Body mass index, mean $\pm$ SD kg/m ² †	30 $\pm$ 7	30 $\pm$ 6	29 $\pm$ 6
White, non-Hispanic race, no. (%)	1,000 (98)	172 (98)	2,982 (97)
Education, no. (%)			
Less than high school	21 (2)	1 (0.6)	61 (2)
High school degree	181 (18)	24 (14)	496 (16)
Technical school	111 (11)	20 (11)	272 (9)
Some college	281 (28)	46 (26)	722 (24)
Bachelor's degree	213 (21)	37 (21)	732 (24)
Graduate degree	201 (20)	43 (25)	736 (24)
Other	15 (2)	4 (2)	42 (1)
Personal smoking			
Never, no (%)	532 (52)	91 (52)	1,796 (59)
Past, no. (%)	431 (42)	77 (44)	1,105 (36)
Current, no. (%)†	60 (6)	7 (4)	160 (5)
Duration of smoking, years	22 (13–31)	26 (12–23)	18 (10–28)
Packs per day	0.8 (0.5–1.5)	0.8 (0.5–0.8)	0.8 (0.5–0.8)
Pack-years	15 (8–29)	19 (10–35)	13 (6–24)
Age started smoking regularly, years	18 (16–19)	18 (16–20)	18 (16–20)
Asthma, no. (%)†	169 (17)	21 (13)	383 (13)
Urban environment, no. (%)	741 (73)	124 (72)	2260 (74)
Any allergy, no. (%)†	643 (64)	112 (65)	1739 (58)
Food	106 (11)	17 (10)	241 (8)
Grass, pollen, or dust	323 (32)	56 (33)	932 (31)
Pets	125 (12)	19 (11)	360 (12)
Insects	76 (8)	11 (6)	228 (8)
Other	380 (38)	67 (39)	957 (32)
Home smoke exposure			
Yes, no. (%)	665 (65)	104 (60)	1890 (62)
Age home smoke exposure started, years	0 (0–15)	0 (0–15)	0 (0–15)
Duration, years	18 (12–21)	20 (16–29)	18 (10–20)
Packs per day	0.8 (0.5–1.5)	0.8 (0.5–1.5)	0.8 (0.5–1.5)
Pack-years	14 (8–27)	17 (9–29)	12 (8–26)
Workplace smoke exposure			
Yes, no. (%)	394 (39)	62 (35)	1105 (36)
Age workplace smoke exposure started, years	25 (17–25)	25 (17–25)	25 (17–25)
Duration, years	10 (5–20)	10 (5–20)	10 (5–19)
Packs per day	0.8 (0.5–1.5)	0.8 (0.5–1.5)	0.8 (0.5–1.5)
Pack-years	8 (4–15)	10 (4–20)	8 (3–15)
Dental visit in previous year, no. (%)†	863 (85)	154 (88)	2646 (87)

* Except where indicated otherwise, values are the median (interquartile range). RA = rheumatoid arthritis.

† Values at time of baseline questionnaire rather than index date.

History of allergy was another exposure of interest in this study. The questionnaire included the query, “Do you have any allergies?” to which participants responded yes or no. If yes,

participants were prompted to mark all allergies that apply: “food allergies such as shellfish or nuts,” “grasses, pollen, or dust,” “pets,” “insect stings or bites,” and/or “other.”

Secondary exposures of interest included history of personal smoking (yes/no), current smoking (yes/no), smoking duration before index date (years), packs per day, and pack-years before index date. Data for all exposures and confounders of interest came from the baseline and follow-up questionnaires. Age, sex, body mass index (BMI), and race were confirmed by the Mayo Clinic medical records, leading to complete data for these fields (27). Obesity was defined as BMI ≥ 30 kg/m².

Statistical analysis. Chi-square tests were used to compare proportions, and Wilcoxon's rank sum tests were used to compare continuous variables. To assess the relationship between each exposure and case/control status, unconditional logistic regression models were used. Sensitivity analyses were performed among the 175 cases of incident RA to allow for interpretation of results with clear timing of exposures before disease and without any possibility of recall bias. An additional sensitivity analysis was performed in the subset of 189 participants with known serologic status, of whom 111 were positive for rheumatoid factor (RF) and/or antibodies to cyclic citrullinated peptide (CCP).

Of the 4,084 study participants, 322 (7.8%) had missing data for at least 1 of the key questionnaire items, including history of asthma, allergy, and personal, home, or workplace smoking exposure. Because of the low frequency of missing data and even lower missingness among each of the individual models, the impact of missing data on the main study results was deemed low. Participants with missing data were excluded from the model pertaining to that exposure. All analyses were prespecified in a protocol unless described as "post hoc." We performed analyses using SAS version 9.4 (SAS Institute), with a 2-sided alpha level of 0.05 as the threshold for significance and 95% confidence intervals (95% CIs).

RESULTS

This study included 1,023 cases of RA from the 55,898 biobank participants. The mean $\pm$ SD age at index date of RA diagnosis for both cases and controls was 50 ± 16 years, while the mean $\pm$ SD age at the time of the baseline survey was 62 ± 13 years. In unadjusted analyses, the RA group included a higher proportion of individuals with a history of personal smoking and allergies, along with increased home smoke exposure pack-years compared to controls (Table 1). Characteristics of the incident RA subgroup were similar to those of the full RA cohort, except for slightly longer duration of smoking before RA and lower frequency of workplace smoke exposure and asthma (Table 1).

In the full study cohort in the unadjusted analysis, asthma was significantly associated with RA (odds ratio [OR] 1.38 [95% CI 1.14–1.68; $P < 0.001$]). This difference remained statistically significant even after controlling for home and workplace smoke exposure, urban environment, and presence of allergies (OR 1.28 [95% CI 1.04–1.58; $P = 0.02$]). However, it was not

Table 2. Association between asthma and RA*

	OR (95% CI)	
	All RA cases (n = 1,023)	Incident RA subset (n = 175)
Unadjusted	1.38 (1.14–1.68)	1.28 (0.75–2.20)
Standard adjustment†	1.37 (1.12–1.67)‡	1.31 (0.74–2.28)
Full adjustment§	1.28 (1.04–1.58)‡	1.17 (0.66–2.06)

* RA = rheumatoid arthritis; OR = odds ratio; 95% CI = 95% confidence interval.

† Adjusted for age, sex, body mass index, race, education, and personal smoking (never/past/current).

‡ $P < 0.05$.

§ Adjusted for allergic disease, urban environment, and home/workplace smoke exposure, in addition to the factors listed above.

statistically significant in the incident RA subset (OR 1.17 [95% CI 0.66–2.06; $P = 0.60$]) (Table 2).

History of any allergy type was also found to be associated with RA in the full study cohort (OR 1.30 [95% CI 1.12–1.51; $P < 0.001$]). Further analyses examined the association of RA among different allergy types. Food allergies in particular were most highly associated with RA (OR 1.38 [95% CI 1.08–1.75; $P = 0.01$]) (Figure 1). The association with allergy was also significant in the incident RA subset (OR 1.61 [95% CI 1.11–2.33; $P = 0.01$]). In particular, a history of food allergy showed a trend toward an increase in the odds of developing RA in the incident RA subset (OR 1.83 [95% CI 0.97–3.45; $P = 0.06$]).

There was no evidence of an association between home or workplace smoke exposure and RA in either the full cohort or the incident RA subset, except for years of home smoke exposure (Table 3). When home and workplace smoke exposure were combined in a post hoc analysis, participants with the highest levels of cumulative passive smoke exposure had

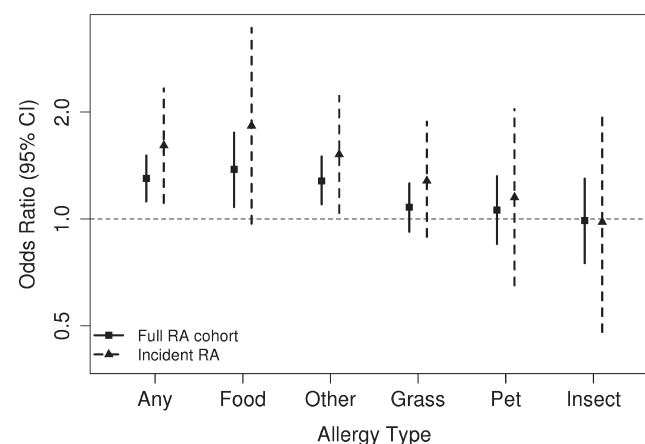


Figure 1. Adjusted association between allergy types and rheumatoid arthritis (RA). Each data point represents a separate model adjusted for age, sex, body mass index, race, education, and personal smoking (never/past/current). Referent is patients without the particular allergy. 95% CI = 95% confidence interval.

increased odds of developing RA in the full cohort (OR 1.37 [95% CI 1.02–1.84]), but not in the incident RA subset (OR 1.34 [95% CI 0.68–2.67]) (Table 3). To determine whether the effect of passive smoke exposure may be higher among nonsmokers, we performed an additional analysis examining the interaction between history of personal smoking (yes or no) and pack-years of home, workplace, and combined home/workplace smoke exposure. There was no evidence that passive smoking

had a different effect among nonsmokers compared to smokers (P for interaction = 0.29, 0.65, and 0.67, respectively).

Personal smoking, and its duration, intensity, and pack-years, were all significant predictors of RA in the full cohort but not in the incident RA subset (Table 4). Age at start of smoking was not associated with an increase in the odds of developing RA in either the full cohort (OR 1.03 [95% CI 1.00–1.06]) or the incident RA cohort (OR 1.00 [95% CI 0.92–1.08]).

Table 3. Adjusted association between passive smoke exposure and RA*

Passive smoke type	Multivariable OR (95% CI)	
	All RA cases (n = 1,023)	Incident RA subset (n = 175)
Home smoke exposure		
Yes	1.06 (0.91–1.23)	0.81 (0.56–1.18)
Age home exposure started†	1.00 (0.99–1.01)	0.99 (0.96–1.01)
Duration, years‡	1.09 (0.99–1.21)	1.37 (1.08–1.72)§
Packs per day	1.12 (0.94–1.01)	1.20 (0.74–1.94)
Pack-years‡	1.03 (0.97–1.09)	1.14 (0.99–1.32)
None (referent)	1.00	1.00
1–9	0.97 (0.78–1.21)	0.63 (0.35–1.17)
10–19	1.13 (0.88–1.45)	0.83 (0.43–1.62)
20–29	1.27 (0.94–1.71)	1.41 (0.68–2.92)
30–39	1.13 (0.71–1.78)	1.07 (0.35–3.34)
40+	1.14 (0.80–1.63)	1.09 (0.47–2.51)
Workplace smoke exposure		
Yes	1.01 (0.86–1.17)	1.04 (0.71–1.52)
Age workplace exposure started†	1.01 (0.99–1.03)	1.03 (0.97–1.07)
Duration, years‡	1.01 (0.85–1.19)	1.05 (0.66–1.67)
Packs per day	1.15 (0.97–1.36)	1.20 (0.74–1.93)
Pack-years‡	1.04 (1.00–1.09)	1.12 (0.83–1.49)
None (referent)	1.00	1.00
1–9	1.01 (0.81–1.26)	0.94 (0.51–1.74)
10–19	0.88 (0.61–1.25)	0.92 (0.38–2.21)
20–29	0.84 (0.46–1.52)	1.12 (0.21–6.09)
30–39	1.80 (1.01–3.19)§	2.36 (0.56–9.94)
40+	1.17 (0.64–2.13)	3.55 (0.64–19.8)
Combined home/workplace smoke exposure		
Pack-years‡	1.04 (1.00–1.09)	1.15 (1.02–1.29)
None (referent)	1.00	1.00
1–9	0.93 (0.74–1.17)	0.65 (0.35–1.21)
10–19	1.08 (0.84–1.39)	0.63 (0.31–1.26)
20–29	1.07 (0.79–1.45)	0.96 (0.46–2.01)
30–39	1.13 (0.76–1.67)	1.07 (0.31–3.76)
40+	1.37 (1.02–1.84)§	1.34 (0.68–2.67)

* Each variable was assessed in a separate model with adjustment for age, sex, body mass index, race, education, and personal smoking (never/past/current). RA = rheumatoid arthritis; 95% CI = 95% confidence interval.

† Adjusted for pack-years of passive smoke exposure, in addition to the factors listed above.

‡ Odds ratios (ORs) reported per 10 units.

§ $P < 0.05$.

Table 4. Adjusted association between personal smoking and RA*

	Multivariable OR (95% CI)	
	All RA cases (n = 1,023)	Incident RA subset (n = 175)
Ever smoked vs. never	1.26 (1.09–1.46)†	1.26 (0.88–1.81)
Current smoker vs. past/never	1.07 (0.78–1.46)	0.68 (0.29–1.59)
Duration, years‡	1.18 (1.06–1.31)†	0.97 (0.77–1.22)
Packs per day	1.20 (1.03–1.40)†	1.06 (0.71–1.58)
Pack-years‡	1.07 (1.01–1.13)†	0.96 (0.84–1.10)

* Each variable was assessed in a separate model with adjustment for age, sex, body mass index, race, education. RA = rheumatoid arthritis; OR = odds ratio; 95% CI = 95% confidence interval.

† $P < 0.05$.

‡ Odds ratios (ORs) reported per 10 units.

Finally, a sensitivity analysis was performed among the subset of patients known to have elevated RF and/or CCP antibodies. Although the group positive for antibodies was small, associations were similar to the main results of the study (see Supplementary Table 3, <http://onlinelibrary.wiley.com/doi/10.1002/art.40858/abstract>). However, there was a suggestion of a stronger association with grass allergy and home smoke exposure (yes or no). Characteristics of patients with missing data are shown in Supplementary Table 4 (<http://onlinelibrary.wiley.com/doi/10.1002/art.40858/abstract>).

DISCUSSION

This study addresses several gaps related to the oral-respiratory hypothesis of RA pathogenesis. Namely, the results support the concept of a marginal association between asthma and RA, identify a connection between allergy and RA, and provide evidence against the notion that passive smoke or earlier age of smoking predisposes individuals to RA.

First, in the full cohort, asthma was associated with RA even after adjustment for allergy and pollutants, which is an association not previously shown. The association between asthma and RA is potentially biologically plausible. Both are immunologic disorders profoundly influenced by environmental factors that induce oxidative stress such as cigarette smoke, wood smoke, and environmental pollution (9–14). Moreover, there are many potential mechanisms that may mediate both disorders, including Th17 inflammation, infectious triggers, premature immune senescence, or other inflammation mediators, such as tumor necrosis factor and leukotrienes (28). However, the strength of association was attenuated after adjustment for newly considered confounders, and the relationship was not statistically significant in the incident RA cohort. Thus, the overall findings from this study reflect the uncertainty of existing literature, with some studies supporting an association between asthma and RA (4–8,29–31) and others refuting such an association (24,32–36).

On the other hand, the presence of a positive association between allergy and RA was initially unexpected, since current immunologic theory segregates RA into the Th1 pathway and allergy into the Th2 pathway (37). A review of older literature shows that the association between allergy and RA was such a strong clinical observation that rheumatologists thought allergy might be involved in the pathogenesis of RA (38,39). Subsequently, several small studies showed no association between atopy and RA (32–34,40,41). More recently, however, several larger cohort studies have repeatedly demonstrated a positive association between allergic disease and RA (5,29,42–44), and a study in The Netherlands showed that parental autoimmunity increased the odds of offspring allergic disease (45). Biologic support for this association includes higher levels of IgE antibodies (46), interleukin-4 production (47), and mast cells (48) in patients with RA. It is possible that as with RA and asthma, a broader problem with immune dysregulation underlies both types of diseases, and having one predisposes to the other.

Passive smoke exposure at home or the workplace, including the age the exposure began, duration, intensity, and pack-years, was not associated with RA. A prior study also showed no evidence of association when combining home and workplace exposure (17). However, because information about the intensity of smoke exposure was not collected in that study, the dose-response effect was not evaluated. When stratifying passive smoke exposure by pack-years, we did find evidence of an association between RA and the highest levels of workplace smoke exposure and combined home and workplace smoke exposure. Thus, high levels of passive smoke exposure may place individuals at higher risk for RA, even among smokers. This finding may explain why an association of passive smoking with RA was suggested in 2 other studies, especially among individuals with a longer duration of exposure extending back to childhood (10,18).

Personal smoking was also associated with RA compared to nonsmoking in the full cohort. This is consistent with findings in previous studies (10,16), which provides reassurance about the validity of our study. However, personal smoking was not associated with RA in our incident RA cohort. There are several potential explanations for this. One is that the incident RA cohort reflects a different subtype of RA, compared to older cases with disease etiology rooted in factors other than smoking. Alternatively, it is possible that there were more subjects who were misclassified in the incident RA group than the full RA cohort, biasing results in that group to the null hypothesis. Thus, it is important to consider both the full RA cohort and the incident RA cohort when interpreting study findings. A novel finding related to personal smoking history was that earlier age of smoking was not associated with increased odds of developing RA. Therefore, earlier age at start of smoking may not be more dangerous compared to start of smoking later in life, with respect to RA risk.

One strength of this study is its large sample size. Another is its detailed questionnaire data. These detailed survey questions provided impressive granularity for the exposures of interest such as personal and passive smoking, and also potential confounders including allergies, urban environment, and educational background. Future studies can leverage not only these questionnaire data, but also the associated lifestyle, clinical, genetic, and serologic data contained within this rich and novel dataset (21).

There are also several important limitations to consider. First, using a convenience sample from clinics rather than a population-based study creates potential selection bias and limits generalizability, even when the population comes mainly from primary care as in this study. Second, recall bias is possible when asking patients about past exposures. However, participants were asked about all comorbidities and exposures both related and unrelated to RA, and the similarity of the results from the incident RA group (which did not have RA at the time of the survey) provides some reassurance. Third, the definition of RA relied partially on self-report, creating potential misclassification bias. Nevertheless, such bias would have reduced any observed associations, and the similarity with incident RA cases was reassuring. Furthermore, the high PPV found with the 2 verification methods provides further reassurance about the rules-based definition of RA used in this study. Finally, for many study participants, data on RA autoantibody status were not available, limiting the number of calculations that could be performed in the sensitivity analysis. Notably, Hedstrom et al showed no difference in the association between passive smoke and RA by antibody status (17).

In conclusion, our results show that asthma and allergies may be associated with increased risk of developing RA, but passive smoke exposure and age at start of smoking are not. Future studies investigating the relationship between RA and early-life atopy are needed.

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AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Kronzer had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Kronzer, Crowson, Sparks, Vassallo, Davis.

Acquisition of data. Kronzer, Crowson, Davis.

Analysis and interpretation of data. Kronzer, Crowson, Sparks, Vassallo, Davis.

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Table S1. Verification of RA definition in a subset of 100 RA cases

Diagnosis	Number
<u>Correct Classification (87%)</u>	
Rheumatoid arthritis	76
Seronegative inflammatory arthritis consistent with RA	11
<u>Incorrect Classification (13%)</u>	
Osteoarthritis	4
No rheumatologic visits or diagnoses	3
Connective tissue disease	1
HLA B27 spondyloarthropathy with inflammatory arthritis	1
Inflammatory arthritis that later resolved	1
Polymyositis	1
"Quiescent RA" which could not be confirmed in the chart	1
Sjogren's-related arthritis, previously diagnosed as RA	1

RA = rheumatoid arthritis

**Table S2. Verification of asthma
classification in a subset of 50 participants**

Asthma classification	Number (%)
Definite asthma	41 (82)
Allergic	16
Cough-variant	4
Exercise-induced	3
Unknown	18
Probable asthma	4 (8)
Possible asthma	1 (2)
No asthma	4 (8)

Table S3. Association between exposures and RA among the CCP/RF positive (N = 111) compared to negative (N = 78) subgroup*

Characteristic	Multivariable OR (95% CI)
Asthma	1.25 (0.47,3.29)
Asthma after further adjustment**	1.21 (0.44,3.39)
Allergy, any	1.31 (0.67,2.55)
Food	1.12 (0.35,3.57)
Grass	2.36 (1.09,5.14)
Pets	0.83 (0.21,3.26)
Insects	0.38 (0.09,1.59)
Other	0.73 (0.36,1.46)
Home smoke exposure, yes	2.28 (1.17,4.42)
Work smoke exposure, yes	0.74 (0.35,1.55)
Ever smoked	1.11 (0.59,2.10)
Current smoker	2.29 (0.58,9.00)

*Reference is CCP/RF negative group. Only models with greater than 50 outcome variables are included. Models adjust for age, sex, body mass index, race, education, personal smoking (never/former/current). Bold values are statistically significant.

**also adjusting for home and work smoke exposure, urban environment, and presence of allergies

CI = confidence interval, CCP = cyclic citrullinated peptide, OR = odds ratio, RF = rheumatoid factor