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Association of sinusitis and upper respiratory tract diseases with incident rheumatoid arthritis: A case-control study

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Abstract

Objective: We aimed to determine whether specific respiratory tract diseases are associated with increased rheumatoid arthritis (RA) risk.

Methods: This case-control study within the Mass General Brigham Biobank matched newly diagnosed RA cases to three controls on age, sex, and electronic health record history. We identified RA using a validated algorithm and confirmed by medical record review. Respiratory tract disease exposure required one inpatient or two outpatient codes at least two years before index date of RA clinical diagnosis or matched date. Logistic regression models calculated odds ratios (OR) for RA with 95% confidence intervals (CI), adjusting for confounders. We then stratified by serostatus ("seropositive" was positive rheumatoid factor and/or anti-citrullinated protein antibodies) and smoking.

Results: We identified 741 RA cases and 2,223 controls (both median age 55, 76% female). Acute sinusitis (OR 1.61, 95% CI:1.05,2.45), chronic sinusitis (OR 2.16, 95% CI:1.39,3.35), and asthma (OR 1.39, 95% CI:1.03,1.87) were associated with increased risk of RA. Acute respiratory tract disease burden during the pre-index exposure period was also associated with increased RA risk (OR 1.30 per 10 codes, 95% CI:1.08,1.55). Acute pharyngitis was associated with seronegative (OR 1.68, 95% CI:1.02,2.74) but not seropositive RA; chronic rhinitis/pharyngitis was associated with seropositive (OR 2.46, 95% CI:1.01,5.99) but not seronegative RA.

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Respiratory tract diseases tended towards higher associations in smokers, especially >10 pack-years (OR 1.52, 95% CI:1.02,2.27; p=0.10 for interaction).

Conclusion: Acute/chronic sinusitis and pharyngitis and acute respiratory burden increased RA risk. The mucosal paradigm of RA pathogenesis may involve the upper respiratory tract.

Keywords

Rheumatoid arthritis; sinusitis; pharyngitis; smoking; epidemiology

INTRODUCTION

Increasing evidence suggests rheumatoid arthritis (RA) may originate at sites of inflamed mucosa such as the lungs. Smoking is the strongest known risk factor for seropositive RA, increasing the odds of disease by two- to threefold (1,2). Exposure to toxins like silica and coal has also been established as a risk for RA.(1,3,4) Chronic lower respiratory tract disease such as asthma (5–12) and chronic obstructive pulmonary disease (COPD) are also established risk factors for RA (6,13,14). A recent case-control study from the Epidemiological Investigation of Rheumatoid Arthritis (EIRA) in Sweden suggested that not only chronic lower respiratory tract diseases like asthma and COPD, but also acute respiratory tract diseases and chronic upper respiratory tract diseases were associated with increased risk of incident RA (15). However, specific acute and/or upper respiratory tract diseases were not studied.

Some studies suggest a possible relationship between certain respiratory tract infections and RA. For example, circulating levels of influenza (16) and measles (17,18) antibodies were higher in patients with prevalent RA compared to controls. However, these studies were cross-sectional with small sample size. Two recent, large cohort studies did how an association between respiratory viral infections (19) and mycoplasma pneumonia (20) with RA risk. However, both only identified hospital-based infections. Furthermore, the former only studied infections 8 weeks to 2 years prior to RA onset even though the RA disease process including RA-related autoantibodies typically develop 2–5 years prior to RA (21,22), while the latter did not adjust for key confounders including smoking and body mass index.

Accordingly, we aimed to determine the association between specific acute and/or upper respiratory tract diseases and RA, including sinusitis, pharyngitis, and pneumonia, using a large cohort of patients with incident RA. We hypothesized that similar to chronic lower respiratory tract diseases, these would be associated with increased risk of RA.

MATERIALS AND METHODS

Study Design

This case-control study leveraged the Mass General Brigham (MGB) Biobank, a research repository from Massachusetts General Hospital, Brigham and Women’s Hospital and their affiliated sites in the greater Boston, Massachusetts area that launched in 2010 (24). As of June 2020, n=117,248 participants had consented to provide blood and agreed to link

their electronic health record (EHR) data and were thus eligible for this study. Participants complete a MGB Biobank health survey that has a 40% response rate (24). This sub-study received approval from the MGB institutional review board (protocol #2019P000264), followed the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) guidelines, and complied with the Declaration of Helsinki.

Incident RA Cases

We initially identified 2,017 adult RA cases in the MGB Biobank using a previously published algorithm for RA that incorporates diagnosis codes, laboratory results, and natural language processing (25,26). This algorithm has a 95% positive predictive value at 97% specificity for RA defined by the 2010 American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) criteria (25). After the initial identification of RA by the algorithm, we verified that all patients in this analysis met 2010 ACR/EULAR RA criteria by medical record review (27). We defined index date as the time of RA clinical diagnosis (or matched date for controls) as indicated by the first interaction with a clinician related to RA symptoms or diagnosis by medical record review. To allow ample time for exposure accrual and improve comparability to the EIRA respiratory study (15), we restricted this analysis to the 741 RA cases with at least five years of preceding medical record data. We identified serostatus in the EHR from clinical laboratory tests using structured data supplemented by manual medical record review. We defined “seropositive RA” as RA with positive rheumatoid factor (RF) and/or anti-citrullinated peptide antibodies (ACPA). We defined shared epitope positivity by presence of HLA-DRB1*04 or HLA-DRB1*01 (28).

Controls

We matched each RA case to three MGB Biobank controls based on age at index date of RA clinical diagnosis (±5 years), sex, and length of prior EHR history (±3 years, as most cases could not be fully matched with ±2 years). We required they had no RA by the algorithm, no billing codes for RA or any other systemic rheumatic disease, and smoking data available from the MGB Biobank questionnaire, since we considered this a key covariate.

Respiratory Tract Disease Exposures

The primary exposure was presence of any respiratory tract disease, as ascertained by International Classification of Diseases (ICD)-9 or ICD-10 diagnosis codes. We also subdivided respiratory exposure by location and acuity of respiratory tract disease (upper and lower, acute and chronic) as well as by specific respiratory tract diseases including acute sinusitis, acute pharyngitis, chronic rhinitis/pharyngitis, chronic sinusitis, pneumonia, asthma, and COPD (Table 1). For all of these respiratory tract exposures, we required at least one code in an inpatient or emergency department setting or at least two outpatient diagnosis codes at least 30 days apart for chronic respiratory tract diseases but without any time requirement for diagnosis of acute respiratory tract diseases.

We also required all these codes to occur at least two years before index date of RA onset or matched date for controls. This requirement reduced the possibility of reverse causation. We selected two years because RA-related autoantibodies appear several years before clinical

onset of RA (21,22). Participants with at least one respiratory tract disease code before index date but not meeting both criteria were defined as “indeterminate” for that particular disease. The reference or “unexposed” group consisted of the participants with no respiratory tract disease code of any kind before index date of RA diagnosis.

A secondary exposure of interest was respiratory tract disease burden. We defined this as the total number of respiratory tract disease codes (continuous), both overall and for acute respiratory tract diseases alone, and studied it in increments of 10 codes. We presumed that the number of codes for chronic respiratory tract diseases would be less useful as it might reflect health care utilization more than true respiratory burden.

To determine the accuracy of using respiratory tract diagnosis codes as the exposures in this study, we performed a manual medical record review of 50 cases of each respiratory tract disease. We defined the gold standard for each respiratory tract disease based on published criteria for each disease (29–33). More specifically, acute sinusitis required up to 4 weeks purulent nasal drainage AND nasal obstruction, facial pain, or both (29), while acute pharyngitis required documented symptoms of throat pain, dysphagia, or nasopharyngitis. Diagnosis of chronic sinusitis required documentation of inflammation PLUS at least two of four sinusitis symptoms for 12 weeks or longer (29). Chronic rhinitis/pharyngitis required consistent symptoms including paroxysms of sneezing, rhinorrhea, nasal obstruction, nasal itching, postnasal drip, cough, throat pain, and/or dysphagia for 12 weeks or longer (30). Pneumonia required demonstrable infiltrate by chest radiograph or other imaging technique (31). Diagnosis of asthma required all three of the following conditions including (1) history of cough with wheezing or dyspnea, (2) variability in symptoms, and (3) at least two supportive measures as defined previously (32). Finally, COPD required forced expiratory volume in one second/forced vital capacity [FEV_1/FVC] ratio less than 0.7 or less than the lower limit of normal [LLN]) that is incompletely reversible after the administration of an inhaled bronchodilator or CT scan showing emphysema (33). The positive predictive values by the gold standard definitions and by physician diagnosis were all high (means 72% and 86%, respectively) (Supplementary Table S1).

Covariates

We chose covariates and potential confounders that were known risk factors for presence of respiratory tract diseases and RA, including age at index date, sex, length of EHR history in the Partners Health system before index date of RA or matched date in years, biobank enrollment year, race/ethnicity (White non-Hispanic vs other), education (four-year college or master’s/doctoral/professional degree vs less), body mass index (BMI; <20, 20-<25, 25-<30, 30+ kg/m^2), and smoking (current, past, never as well as continuous pack-years, all as of MGB Biobank enrollment on the health survey). Length of EHR history, sex, race/ethnicity, and BMI came from EHR data. We obtained enrollment year, education, and smoking data from MGB Biobank enrollment survey data. To determine missing BMI and smoking data, we performed manual medical review.

Statistical Analysis

We used chi-square tests to compare proportions and Wilcoxon rank sum tests with medians and interquartile ranges (IQR) to compare continuous variables between cases and controls. For participants with missing education (15%), we used logistic regression imputation to predict high or low educational level as a function of sex, case/control status, and race. All other covariates had no missing data. For our primary analysis, we used multivariable conditional logistic regression models to calculate odds ratios (OR) with 95% confidence intervals (CI) for the association between each respiratory tract disease and incident RA. We examined any respiratory tract disease, specific respiratory tract diseases, and respiratory tract disease burden, as detailed above. The models adjusted for age, sex, length of EHR history, biobank enrollment year, race/ethnicity, education, BMI, smoking status, and smoking pack-years.

We also conducted stratified analysis by RA serostatus. We compared seropositive RA cases only to their matched comparators so that the matching was preserved. Patients with missing RA-related autoantibodies were excluded. We also performed stratified analyses based on smoking status (ever or never) and smoking pack-years (never smoker, >0 to 10 pack-years, and >10 pack-years). To investigate whether the relationship between respiratory tract diseases and RA varied by smoking status, we tested for multiplicative interactions between each respiratory tract disease and smoking for risk of RA. All the above analyses were pre-specified in our protocol and performed using SAS version 9.4 (SAS Institute Inc., Cary, NC) except for logistic regression imputation, for which we used R Core Team (2020) MICE package (R Foundation for Statistical Computing, Vienna, Austria). We considered two-sided $p<0.05$ as statistically significant.

RESULTS

Study Sample Characteristics

This study included 741 incident RA cases and 2,223 matched controls (median age 55, 76% female). Compared to controls, RA cases were more likely to have slightly longer EHR history, non-White or Hispanic race, lower education, higher BMI, and higher smoking exposure (Table 2). Median time from index date to biobank enrollment was 3.15 years for RA cases (IQR 0.55 to 8.12) and 4.04 years for controls (IQR 0.54 to 8.55) ($p=0.26$). Among the 741 RA cases, 426 (57%) were seropositive, 303 (41%) were seronegative, and 12 (1.6%) had no available test results for RF or ACPA. Within the 346 (47%) of RA cases with genotyping data available, 200 (58%) were positive for the shared epitope.

Respiratory Tract Diseases and RA

Any respiratory disease exposure occurred in 346 (47%) of the RA cases and 931 (42%) of the controls ($p=0.007$). After adjusting for covariates, specific respiratory tract diseases including acute sinusitis (OR 1.61 95% CI 1.05 to 2.45), chronic sinusitis (OR 2.16, 95% CI 1.39 to 3.35), and asthma (OR 1.39, 95% CI 1.03 to 1.87) were associated with increased odds of RA (Table 3). Acute respiratory tract disease burden was associated with increased odds of newly diagnosed RA (OR 1.30 per 10 codes, 95% CI 1.08 to 1.55). Overall burden of respiratory tract disease, as assessed by total number of respiratory tract disease diagnosis

codes, was not associated with increased risk of RA (OR 1.01 per 10 codes, 95% CI 0.98 to 1.05). Of note, “indeterminate” respiratory tract disease exposures were not associated with RA (data not shown).

Results by RA Serostatus

Overall, the association between respiratory tract diseases and RA was similar for seropositive and seronegative RA (p for interaction 0.60 for any respiratory disease, and p>0.05 for all individual respiratory tract exposures, Table 3). Some respiratory tract diseases, including acute sinusitis and chronic rhinitis/pharyngitis, were associated only with seropositive RA (OR 1.89, 95% CI 1.03 to 3.49 and OR 2.46, 95% CI 1.01 to 5.99, respectively) (Table 3). Others, including acute pharyngitis and chronic sinusitis, were associated only with seronegative RA (OR 1.68, 95% CI 1.02 to 2.74 and OR 3.23, 95% CI 1.65 to 6.32, respectively) (Table 3). In a post-hoc analysis, the association between respiratory diseases and seropositive RA did not differ substantially when restricting to cases with ACPA greater than twice the upper limit of normal (Supplementary Table S2).

Stratification by Smoking

Just like serostatus, the interaction between respiratory exposure and smoking was not statistically significant (p=0.10 for any respiratory disease, and p>0.05 for all individual respiratory tract exposures). By point estimates, however, nearly every respiratory exposure was more strongly associated with RA in smokers than in nonsmokers (Table 4). Stratifying by smoking pack-years revealed that respiratory tract diseases tended to be associated with increased risk of RA only in individuals who had smoked greater than 10 pack-years, but p for interaction were all >0.05 (Table 5).

DISCUSSION

This large case-control identified acute and chronic sinusitis and pharyngitis as risk factors for incident RA. Acute respiratory tract disease burden increased risk of RA as well. The association between respiratory tract diseases and RA occurred for both seropositive and seronegative RA and was strongest in smokers. These results extend the mucosal paradigm for RA pathogenesis to include the upper respiratory tract and necessitate further epidemiologic, microbial, and genetic studies of this novel anatomic site for RA-related autoimmunity.

The association between upper airway disease and RA has not been previously reported. While no prior studies have directly examined pharyngitis and risk of RA, a recent study did show that three types of upper respiratory viruses (coronavirus, parainfluenza, and metapneumovirus) increased risk of incident RA (19). This study therefore provides further rationale to investigate whether SARS-CoV-2 could impact RA risk even after the resolution of acute infection (34,35). A meta-analysis restricted to high-quality studies of allergic rhinitis also showed an association with RA (23), supporting our findings for chronic pharyngitis/rhinitis. The single previous study of sinusitis showed no association with RA, but it used self-reported diseases only within two years of RA onset (36). Overall, these

results suggest that the upper airway may be a novel mucosal site of RA origination, but will require replication.

The total burden of acute respiratory tract diseases also increased the risk of RA. While the point estimate was modest, many acute respiratory tract diseases do not come to medical attention, which could bias results toward the null. No prior studies have examined respiratory tract burden and RA risk. Although these novel findings will require replication, they suggest that interventions to reduce respiratory tract diseases including masking, handwashing, and vaccination could impact RA risk.

The finding that so many different respiratory tract disease types are now associated with RA raises the question of whether the relationship is truly causal or confounded as an epiphenomenon. For example, broader immune system dysregulation could predispose to both respiratory tract diseases and RA, with the respiratory tract diseases simply manifesting first. However, even non-infectious respiratory tract diseases like asthma (5–12) and COPD (6,13,14) have been consistently shown to be associated with RA. Furthermore, respiratory tract diseases including asthma (37), COPD (38), and interstitial lung disease (39) have been shown to generate ACPA. Overall, our results support a growing body of evidence that implicates the oral and respiratory mucosa in RA pathogenesis (40). Future studies examining the timing between respiratory tract diseases and RA onset could also help determine the likelihood of causality and optimal window for prevention.

In this study, the association between respiratory tract diseases and RA was stronger in heavy smokers than in nonsmokers for all respiratory tract disease types. A similar study using EIRA suggested the reverse association (15), whereas another study of asthma alone showed no difference in association by smoking status (6). Besides chance, one reason for this discrepancy could be that this study selected controls with presence of smoking data. As a result, more controls might have been nonsmokers, giving the illusion that the association between respiratory tract disease and RA occurred more often in smokers. Unlike the EIRA study, our study also required a two-year lag between exposure and RA. The interaction between smoking and respiratory tract disease may act differently for recent compared to distant respiratory tract diseases in relation to timing of RA onset. Other possibilities include population differences. For example, the gene-environment interaction between smoking and the shared epitope is strong in Sweden (28,41,42), but this has not been consistently replicated in North America (43,44). Population genetic differences may underlie this discrepancy, which could contribute to different mechanisms of RA pathogenesis. Further studies of respiratory tract diseases and smoking in combination with RA genetics are needed.

Strengths of this study include its large sample size, incident RA cases, manual verification of RA and the timing of RA onset, data on RA serological status, and adjustment for many important confounders including smoking. Limitations of this study first include the potential for selection bias among MGB Biobank participants, who may differ from the surrounding general population—especially those who answered the health survey. In addition, this population of participants may not generalize to other populations outside of the greater Boston area and/or White non-Hispanic race. These population differences

could bias results either toward or away from the null. Second, the sample size precluded study of certain diseases of interest such as influenza and interstitial lung disease. Third, misclassification of respiratory tract disease exposures is possible. Although the positive predictive values were high, these codes did not capture events that occurred outside the MGB system or early life exposures. However, this form of misclassification would bias exposures and observed effects towards the null. Fourth, residual confounding for is possible. For example, we did not adjust for pollution or other inhalational agents, and smoking status measured at time of MGB Biobank enrollment may not reflect the precise smoking history prior to RA, though this would be more likely to affect smoking pack-years than smoking status. Fifth, reverse causation, where RA increases risk of respiratory tract diseases is possible. Although we required respiratory tract diseases to occur at least two years before date of clinical onset of RA, further investigation of the association of timing of respiratory tract exposures and RA is warranted. Finally, our analyses did not adjust for multiple comparisons and thus require replication.

Conclusion

In summary, we identified sinusitis, pharyngitis, and acute respiratory tract burden as potential novel risk factors for RA. These findings extend the mucosal hypothesis of RA pathogenesis to the upper airway. Future studies should investigate whether additional upper respiratory tract diseases such as SARS CoV-2 are associated with RA and define the timing, microbiology, and genetic underpinning of these associations.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1.

Respiratory tract exposures and their corresponding International Classification of Disease (ICD) codes

Respiratory tract diseases	ICD-10	ICD-9
All respiratory tract diseases	J00-J99	460–519
Acute upper respiratory tract diseases	J00-J06, J36	460–465, 475
Acute sinusitis	J01	461
Acute pharyngitis or nasopharyngitis	J02, J00	462, 460
Chronic upper respiratory tract diseases	J30-J35, J37-J39	470–474, 476–478
Chronic rhinitis and pharyngitis	J31	472
Chronic sinusitis	J32	473
Acute lower respiratory tract diseases	J09-J18, J20-J22, J69	466, 480–488, 507
Pneumonia	J12-J18	480–486
Chronic lower respiratory tract diseases	J40-J47, J60-J64, J66–67, J82, J84	490–495, 500–505, 515–516, 518.3
Asthma	J45-J46	493
Chronic obstructive pulmonary disease	J40-J44	490, 491.0, 491.1, 491.2, 491.8, 492, 496

Table 2.

Characteristics of the 741 incident Mass General Brigham Biobank RA cases and 2,223 matched controls with at least 5 years of EHR history, at index date of RA diagnosis

Characteristic	RA cases (n=741)	Controls (n=2,223)	p-value
Age in years, median (IQR)	55 (45,63)	56 (47,63)	0.46 *
Female sex, n (%)	563 (76)	1689 (76)	1.00 *
EHR history in years, median (IQR)	12 (8,16)	11 (8,16)	0.004 *
Enrollment year, median (IQR)	2016 (2014,2017)	2016 (2014,2017)	0.04
White, non-Hispanic race, n (%)	597 (81)	2015 (91)	<0.001
Education college or higher, n (%) **	485 (65)	1600 (72)	<0.001
BMI, kg/m^2, n (%)			<0.001
<20	24 (3)	124 (6)	
20–25	221 (30)	753 (34)	
25–30	216 (29)	688 (31)	
30+	280 (38)	658(30)	
Smoking status, n (%) **			<0.001
Never	366 (49)	1240 (56)	
Past	303 (41)	862 (39)	
Current	72 (10)	121 (5)	
Smoking pack-years, n(%)			<0.001
0 (nonsmoker)	366 (49)	1240 (56)	
1–10	178 (24)	579 (26)	
>10	197 (27)	404 (18)	

BMI = body mass index, CI = confidence interval, EHR = electronic health record, IQR = interquartile range, kg = kilograms, m = meters, RA = rheumatoid arthritis

* Matching factor

** As of Mass General Brigham Biobank enrollment

Table 3.

Associations between preceding respiratory tract diseases (at least two years before index date) and incident RA

	Number (%)		Adjusted* Odds Ratio for RA (95% CI)		
	RA cases (n=741)	Controls (n=2,223)	All RA cases (n=741)	Seropositive RA cases (n=426)**	Seronegative RA cases (n=303)
Any respiratory tract disease	346 (47)	931 (42)	1.16 (0.95,1.42)	1.14 (0.87,1.50)	1.24 (0.92,1.69)
Acute upper	171 (23)	432(19)	1.25 (0.98,1.60)	1.24 (0.88,1.74)	1.36 (0.94,1.97)
Acute sinusitis	45 (6)	86 (4)	**1.61 (1.05,2.45)**	**1.89 (1.03,3.49)**	1.43 (0.77,2.64)
Acute pharyngitis	80(11)	192 (9)	1.34 (0.97,1.85)	1.18 (0.75,1.85)	**1.68 (1.02,2.74)**
Chronic upper	104 (14)	286 (13)	1.18 (0.89,1.56)	1.12 (0.76,1.65)	1.30 (0.85,2.00)
Chronic sinusitis	42 (6)	68 (3)	**2.16 (1.39,3.35)**	1.55 (0.83,2.88)	**3.23 (1.65,6.32)**
Chronic rhinitis/ pharyngitis	17 (2)	33 (1)	1.77 (0.95,3.27)	**2.46 (1.01,5.99)**	1.56 (0.63,3.88)
Acute lower	78 (11)	153 (7)	1.37 (0.98,1.91)	1.46 (0.94,2.28)	1.30 (0.76,2.20)
Pneumonia	38 (5)	87 (4)	1.17 (0.76,1.81)	1.00 (0.54,1.87)	1.53 (0.81,2.86)
Chronic lower	121 (16)	263(12)	**1.32 (1.01,1.74)**	1.24 (0.85,1.81)	1.49 (0.99,2.23)
Asthma	93 (13)	193 (9)	**1.39 (1.03,1.87)**	1.35 (0.89,2.05)	1.49 (0.96,2.31)
COPD	43 (6)	83 (4)	1.35 (0.88,2.06)	1.20 (0.67,2.15)	1.55 (0.82,2.93)

BMI = body mass index, CI = confidence interval, COPD = chronic obstructive pulmonary disease, RA = rheumatoid arthritis

*Respiratory codes at least two years before index date of RA or matched date. Reference group was individuals with no respiratory tract disease codes of any kind prior to index date. Adjusting for age, sex, EHR history, enrollment year, race/ethnicity, education, BMI, smoking status, and pack-years. Bold values are statistically significant.

**RA cases without RA-related autoantibody test results (n=12) could not be classified by serostatus. Their n=36 matched controls were also removed from these analyses.

Table 4.

Associations between preceding respiratory tract diseases (at least two years before index date) and incident RA, stratified by smoking status

	Adjusted* Odds Ratio for RA (95% CI)	
Respiratory tract disease	**Nonsmokers (n=1,606)**	**Ever smokers (n=1,358)**
Any respiratory tract disease	1.02 (0.77,1.34)	1.10 (0.84,1.45)
Acute upper	0.97 (0.69,1.36)	1.21 (0.86,1.70)
Acute sinusitis	1.35 (0.74,2.44)	1.51 (0.88,2.60)
Acute pharyngitis	0.87 (0.56,1.36)	1.42 (0.90,2.22)
Chronic upper	1.01 (0.69,1.47)	1.06 (0.71,1.59)
Chronic sinusitis	**1.86 (1.05, 3.29)**	1.82 (0.98,3.38)
Chronic rhinitis/pharyngitis	1.71 (0.79,3.72)	1.10 (0.38,3.19)
Acute lower	1.20 (0.75,1.93)	1.46 (0.94,2.27)
Pneumonia	1.07 (0.57,2.03)	1.30 (0.74,2.28)
Chronic lower	1.18 (0.81,1.73)	1.31 (0.89,1.91)
Asthma	1.23 (0.82,1.84)	1.28 (0.83,1.98)
COPD	1.53 (0.77,3.04)	1.46 (0.88,2.44)

BMI = body mass index, CI = confidence interval, COPD = chronic obstructive pulmonary disease, RA = rheumatoid arthritis

*Respiratory codes at least two years before index date of RA or matched date. Reference group was individuals with no respiratory tract disease codes of any kind prior to index date. Adjusting for age, sex, EHR history, enrollment year, race/ethnicity, education, BMI. The ever smoker analysis was additionally adjusted for smoking status (past/current) and pack-years. Bold values are statistically significant.

Table 5.

Associations between preceding respiratory tract diseases (at least two years before index date) and incident RA, stratified by smoking pack-years

Respiratory tract disease	Nonsmokers (n=1,606)	>0 to 10 Pack-Years (n=757)	>10 Pack-Years (n=601)
Any respiratory tract disease	1.02 (0.77,1.34)	0.81 (0.55,1.19)	**1.52 (1.02,2.27)**
Acute upper	0.97 (0.69,1.36)	0.85 (0.53,1.37)	**1.80 (1.08,2.97)**
Acute sinusitis	1.35 (0.74,2.44)	1.19 (0.55,2.61)	1.94 (0.89,4.25)
Acute pharyngitis	0.87 (0.56,1.36)	1.04 (0.57,1.91)	**2.22 (1.10,4.50)**
Chronic upper	1.01 (0.69,1.47)	0.67 (0.37,1.23)	1.69 (0.94,3.02)
Chronic sinusitis	**1.86 (1.05, 3.29)**	0.54 (0.18,1.64)	**4.90 (1.93,12.42)**
Chronic rhinitis/pharyngitis	1.71 (0.79,3.72)	0.25 (0.03,1.95)	**
Acute lower	1.20 (0.75,1.93)	0.62 (0.30,1.32)	**2.49 (1.37,4.53)**
Pneumonia	1.07 (0.57,2.03)	0.68 (0.28,1.69)	2.14 (0.99,4.64)
Chronic lower	1.18 (0.81,1.73)	0.97 (0.56,1.69)	1.71 (0.99,2.94)
Asthma	1.23 (0.82,1.84)	1.12 (0.62,2.02)	1.54 (0.80,2.96)
COPD	1.53 (0.77,3.04)	0.55 (0.19,1.55)	**2.00 (1.06,3.77)**

BMI = body mass index, CI = confidence interval, COPD = chronic obstructive pulmonary disease, RA = rheumatoid arthritis

* Respiratory codes at least two years before index date of RA or matched date. Reference group was individuals with no respiratory tract disease codes of any kind prior to index date. Adjusting for age, sex, EHR history, enrollment year, race/ethnicity, education, BMI. Bold values are statistically significant.

** Model did not converge