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ORIGINAL RESEARCH

Association between sinusitis and incident rheumatic diseases: a population-based study

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ABSTRACT

Objectives To determine whether antecedent sinusitis is associated with incident rheumatic disease.

Methods This population-based case–control study included all individuals meeting classification criteria for rheumatic diseases between 2002 and 2014. We matched three controls to each case on age, sex and length of prior electronic health record history. The primary exposure was presence of sinusitis, ascertained by diagnosis codes (positive predictive value 96%). We fit logistic regression models to estimate ORs for incident rheumatic diseases and disease groups, adjusted for confounders.

Results We identified 1427 incident rheumatic disease cases and 4281 matched controls (mean age 63, 67% women, median 14 years electronic health record history). After adjustment, preceding sinusitis was associated with increased risk of several rheumatic diseases, including antiphospholipid syndrome (OR 7.0, 95% CI 1.8 to 27), Sjögren's disease (OR 2.4, 95% CI 1.1 to 5.3), and any rheumatic disease (OR 1.4, 95% CI 1.2 to 1.7). Acute sinusitis was also associated with increased risk of seronegative rheumatoid arthritis (OR 1.8, 95% CI 1.1 to 3.1). Sinusitis was most associated with any rheumatic disease in the 5–10 years before disease onset (OR 1.7, 95% CI 1.3 to 2.3). Individuals with seven or more codes for sinusitis had the highest risk for rheumatic disease (OR 1.7, 95% CI 1.2 to 2.4). In addition, the association between sinusitis and incident rheumatic diseases showed the highest point estimates for never smokers (OR 1.7, 95% CI 1.3 to 2.3).

Conclusions Preceding sinusitis is associated with increased incidence of rheumatic diseases, suggesting a possible role for sinus inflammation in their pathogenesis.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Respiratory irritants are associated with incidence of many rheumatic diseases.

WHAT THIS STUDY ADDS

⇒ In this population-based case–control study, preceding sinusitis was associated with 1.4-fold increased odds of any rheumatic disease, especially antiphospholipid syndrome (7.0-fold increased odds) and Sjögren's disease (2.4-fold increased odds). In general, the association was strongest in the 5–10 years before disease onset and increased in a dose-response fashion with the number of sinusitis codes.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Sinusitis may play a role in the pathogenesis of rheumatic diseases. Therefore, it represents a novel potential target for disease prevention and/or treatment.

INTRODUCTION

Respiratory irritants such as cigarette smoking have been associated with development of nearly all autoimmune rheumatic diseases including ankylosing spondylitis (AS),[1] giant cell arteritis (GCA),[2] myositis,[3] psoriatic arthritis (PsA),[4] rheumatoid arthritis (RA)[5] and systemic lupus erythematosus (SLE).[6] Silica exposure has also been associated with several rheumatic diseases including vasculitis,[7] RA,[8] SLE[9] and systemic sclerosis (SSc).[10] Many other diverse forms of pulmonary irritation are associated with RA pathogenesis including air pollutants,[11] occupational inhalational exposures[12] and respiratory tract diseases.[13]

Building off this prior work, we recently identified an association of upper respiratory tract diseases such as sinusitis with increased risk of incident seropositive and seronegative RA.[14] This association was strongest in the 5–10 years before RA onset, where acute sinusitis was associated with fourfold increased risk of RA.[15] This association is plausible given the known association between sinusitis and antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis.[16] Furthermore upper respiratory tract diseases are associated with

incident myositis,[17] and infections are associated with GCA,[18 19] Sjögren's disease[20] and SLE.[21] Despite all of this evidence, the association between sinusitis and rheumatic diseases other than RA and ANCA-associated vasculitis remains unstudied.

To address this gap, we first aimed to determine the association between preceding history of sinusitis and later incidence of rheumatic diseases. Second, we aimed to determine the association between the timing of sinusitis and incidence of rheumatic diseases. We hypothesised that sinusitis is associated with an increased risk of most rheumatic diseases, especially in the 5–10 years before disease onset and for GCA, Sjögren's and SLE given their previously identified association with infections.

METHODS

Study design and participants

This population-based case–control study leveraged the Rochester Epidemiology Project (REP), a medical records-linkage system of over 500 000 unique individuals who resided in Olmsted County, Minnesota at some point between 1966 and the present.[22] This study included adult subjects from the start of the electronic health record (EHR) on 1 January 1995 until 12 December 2014—the last date where all REP rheumatic disease cohorts were updated. To allow ample time for exposure accrual, we *a priori* restricted the primary analysis to individuals with at least 7 years of EHR data before the index date of rheumatic disease criteria fulfilment or matched date for controls. This study complies with the Declaration of Helsinki.

Patient and public involvement

Patients and the public were involved in the creation of the REP but were not involved in the design or conduct of this particular analysis.

Incident rheumatic disease cases

All individuals with incident rheumatic diseases in this study met published classification criteria for ANCA-associated vasculitis,[23] primary or secondary antiphospholipid syndrome (APS),[24] AS,[25] dermatomyositis,[26] GCA,[27] mixed connective tissue disease (MCTD),[28] polymyalgia rheumatica (PMR),[29] PsA,[30] RA[31] or SLE.[32] The two exceptions were Sjögren's disease (due to the low frequency of lip biopsy) and SSc, which were based on physician diagnosis.[33 34] We studied any disease with at least 20 subjects individually. We also combined all these diseases into standard disease groups including systemic autoimmune rheumatic disease (APS, dermatomyositis, MCTD, SLE, Sjögren's disease, SSc, spondyloarthritis (AS and PsA) and vasculitis (ANCA, GCA and PMR). We defined seropositive RA as positive rheumatoid factor (RF) and/or anti-cyclic citrullinated peptide (CCP) antibodies. Individuals that met criteria for more than one rheumatic disease were included only in the disease cohort where they first met criteria.

Controls

We matched each incident rheumatic disease case to three controls based on age (±5 years) at index date, sex and length of prior EHR history (±3 years). As for cases, we required that controls have at least 7 years EHR data. We also required controls to have no diagnosis codes for any rheumatic disease, as shown in eTable 1 in the supplement online supplemental file S1.[23 35]

Sinusitis exposures

The primary exposure for this study was presence of any sinusitis (also subdividing into acute and chronic sinusitis). To reduce the likelihood of reverse causation, we required sinusitis to occur at least 1-year prior to index date. We ascertained presence of sinusitis using International Classification of Diseases (ICD) diagnosis codes for acute (ICD-9 461) or chronic (ICD-9 473) sinusitis, as described previously.[14 15] The secondary exposure of interest was timing of the first occurrence of sinusitis, defined as the date of meeting the above exposure criteria. We subdivided these durations into >1 to 5 years, 5 to 10 years and >10 years. The reference or 'unexposed' group throughout this study consisted of the individuals with no sinusitis code of any kind between 1 January 1995 and the index date.

Our previous study in the Mass General Brigham Biobank showed the above definitions for acute and chronic sinusitis had a positive predictive value (PPV) of 96% and 88% by physician diagnosis and 80% and 62% by gold standard published criteria,[36 37] respectively.[14] We performed a separate validation in the REP using 50 randomly selected study subjects with sinusitis exposure (25 acute and 25 chronic sinusitis). Once again, we used physician diagnosis as the reference standard and validated these definitions by published criteria.[36 37]

Covariates

We chose covariates based on prior association with rheumatic diseases and obtained them from the EHR's patient provided information. These included age at index date (continuous), sex (male, female), length of EHR history prior to index date (continuous), race and ethnicity (Asian, black, Hispanic (regardless of race), white, other/not reported), body mass index (BMI) at index date (continuous) and smoking status at index date (never, past, current). We obtained RA serostatus from EHR laboratory data. Missing BMI, smoking status and RA serostatus were imputed using 25 multiple imputed data sets. No subjects were missing any other data.

Statistical analysis

We summarised categorical variables as frequencies and continuous variables as means or medians. To estimate the association between sinusitis and rheumatic disease, we fit multivariable conditional logistic regression models. These models estimated ORs with 95% CIs for each rheumatic disease and disease group associated with sinusitis exposure (any, acute and chronic). Models were

adjusted for age, sex, EHR history, race and ethnicity, BMI and smoking status, as long as at least 56 rheumatic disease outcomes were present.[38] If not, we reported estimates from unadjusted conditional logistic models (conditioned on matching factors). To estimate the association between timing of sinusitis and each rheumatic disease, we fit the same models above but with the time window of first sinusitis exposure (>1 to 5 years, >5 to 10 years and >10 years) as the exposure.

We also performed three sensitivity analyses. First, we relaxed the 7-year EHR history requirement to only 3 years. Second, to determine if the burden of sinusitis was associated with each rheumatic disease, we repeated the above models with the number of qualifying sinusitis codes (1–3, 4–6 or 7+) as the exposure of interest. Third, given the strong association between smoking and many of the rheumatic diseases we studied, we estimated the association between sinusitis and disease according to smoking status (ever vs never) in pre-planned interaction analyses. Throughout this study, we used a significance threshold of two-sided alpha=0.05. We prespecified all analyses in a study protocol. All analyses were conducted using R V.4.1.2 (R Foundation for Statistical Computing, Vienna, Austria) and SAS V.9.4 (SAS Institute, Cary, North Carolina, USA).

RESULTS

Cohort characteristics

This study included 1427 incident rheumatic disease cases and 4281 matched controls (mean age 61, 67% women and median EHR history duration 14 years in both groups). The median duration from first sinusitis code to index date of rheumatic disease criteria fulfilment was 7.9 years (IQR 4.3–10.7). Sinusitis codes had a 96% PPV (96% acute; 96% chronic) by physician diagnosis and 60% PPV (68% acute; 52% chronic) by gold-standard published criteria. The most common rheumatic disease in this cohort was RA (n=688), followed by PMR (n=308, table 1), whereas the least common were dermatomyositis (n=12) and MCTD (n=16). Among RA cases, 452 (66%) were seropositive, 234 (34%) were seronegative and 2 (0.3%) were unknown. The only other missing data among cases and controls were BMI in 190 (3.3%) and smoking status in 225 (3.9%).

Sinusitis and incident rheumatic disease

In multivariable analysis, history of sinusitis was associated with increased risk of any incident rheumatic disease (OR 1.4, 95% CI 1.2 to 1.7, table 2). This association was strongest for systemic autoimmune rheumatic diseases such as APS (OR 7.0, 95% CI 1.8 to 27) and Sjögren's disease (OR 2.4, 95% CI 1.1 to 5.3, table 2). Acute sinusitis also showed a significant association with seronegative RA (OR 1.8, 95% CI 1.1 to 3.1). A sensitivity analysis repeating the above results but relaxing the EHR history requirement to only 3 years produced nearly identical results (eTable 2 in the supplement online supplemental file 1).

Association by timing of sinusitis

The association between sinusitis and incident rheumatic disease showed the strongest point estimates in the 5–10 years before rheumatic disease onset (OR 1.7, 95% CI 1.3 to 2.3, table 3). Acute sinusitis was associated with any rheumatic disease only in the 5–10 years before disease onset (OR 1.5, 95% CI 1.0 to 2.2), whereas chronic sinusitis was associated in both the 1–5 years (OR 1.9, 95% CI 1.3 to 2.9) and 5–10 years (OR 1.7, 95% CI 1.2 to 2.4) before rheumatic disease onset. This stronger association between sinusitis and rheumatic diseases in the 5–10 years window before disease was especially evident for Sjögren's disease (OR 3.2, 95% CI 1.1 to 9.5) and PMR (OR 2.0, 95% CI 1.0 to 3.8, table 3). In contrast, sinusitis showed a stronger association with APS and RA in the 1–5 years before disease onset (table 3).

Association by number of sinusitis codes

The number of sinusitis codes showed a statistically significant dose-response relationship with incidence of rheumatic disease (table 4). For example, individuals with seven or more codes for sinusitis had strongly elevated risk for incident systemic autoimmune rheumatic disease (OR 4.8, 95% CI 1.7 to 13), Sjögren's disease (OR 8.7 95% CI 1.4 to 52) and vasculitis (OR 2.1, 95% CI 1.1 to 4.2). Acute sinusitis also showed a significant dose-response association for seronegative RA (OR 0.8 95% CI 0.3 to 2.1 for 1–2 codes, OR 1.9 95% CI 0.8 to 4.0 for 3–4 codes and OR 4.3, 95% CI 1.6 to 11 for 5+ codes, p=0.01).

Association by smoking status

The association between sinusitis and any incident rheumatic disease was higher for never smokers (OR 1.7, 95% CI 1.3 to 2.3) compared with ever smokers (OR 1.2, 95% CI 0.9 to 1.5, p=0.039, table 5). Indeed, sinusitis was associated with higher point estimates among never smokers in most individual rheumatic diseases and disease groups (table 5), including RA (OR 1.6, 95% CI 1.1 to 2.4 for never smokers, OR 1.1 95% CI 0.8 to 1.5 for ever smokers). Sjögren's disease was the only disease where sinusitis was statistically significantly associated in ever smokers (OR 2.9, 95% CI 1.0 to 8.2) but not in never smokers (OR 2.1, 95% CI 0.7 to 6.1).

DISCUSSION

In this population-based cohort of incident rheumatic disease cases and controls, preceding sinusitis was associated with increased risk of multiple incident rheumatic diseases, especially APS and Sjögren's disease. In general, the association between sinusitis and rheumatic diseases was strongest in the 5–10 years before disease onset and increased in a dose-response fashion with the number of sinusitis codes. Finally, the association between sinusitis and rheumatic disease was stronger among never

Table 1 Characteristics of the 1729 incident rheumatic disease cases in the Rochester Epidemiology Project with at least 7 years EHR history

Characteristic	ANCA vasculitis (n=38)	Ankylosing spondylitis (n=22)	APS (n=26)	Giant cell arteritis (n=79)	PMR (n=308)	Psoriatic arthritis (n=91)	RA (n=688)	Sjögren's syndrome (n=74)	SLE (n=44)	Systemic sclerosis (n=29)	All cases (n=1427)	Controls (n=4281)
Age, years, mean (SD)	60 (16)	35 (10)	59 (17)	78 (9)	74 (9)	47 (11)	57 (15)	61 (15)	50 (18)	60 (15)	61 (16)	61 (16)
Female sex, n (%)	18 (47)	9 (41)	13 (50)	60 (76)	193 (63)	40 (44)	479 (70)	60 (81)	34 (77)	25 (86)	954 (67)	2862 (67)
EHR history, years, median (IQR)	13 (10–17)	11 (8–12)	12 (9–16)	14 (11–17)	13 (10–16)	13 (9–16)	15 (11–17)	12 (10–16)	16 (12–18)	13 (11–16)	14 (10–17)	14 (10–17)
Race and ethnicity, n (%)												
Asian	0 (0)	2 (9)	0 (0)	0 (0)	3 (1)	2 (2)	18 (3)	0 (0)	0 (0)	2 (7)	27 (2)	115 (3)
Black	0 (0)	0 (0)	0 (0)	0 (0)	3 (1)	3 (3)	10 (1)	1 (1)	1 (2)	0 (0)	18 (1)	79 (2)
Hispanic	1 (3)	2 (9)	0 (0)	1 (1)	4 (1)	5 (5)	26 (4)	3 (4)	1 (2)	0 (0)	43 (3)	143 (3)
White	34 (89)	18 (82)	25 (96)	78 (99)	292 (95)	80 (88)	629 (91)	70 (95)	41 (93)	25 (86)	1320 (93)	3864 (90)
Other/not reported	3 (8)	0 (0)	1 (4)	0 (0)	6 (2)	1 (1)	5 (1)	0 (0)	1 (2)	2 (7)	19 (1)	80 (2)
BMI, kg/m^2, median (IQR)	27 (24–32)	26 (24–31)	29 (25–33)	26 (22–29)	27 (24–31)	31 (27–35)	29 (25–33)	26 (22–32)	30 (26–34)	28 (24–31)	28 (25–32)	28 (24–32)
Smoking status, n (%)												
Never	9 (26)	12 (57)	11 (42)	36 (46)	136 (45)	29 (32)	249 (37)	30 (41)	14 (33)	8 (29)	549 (39)	1816 (44)
Past	21 (60)	5 (24)	10 (38)	39 (50)	147 (48)	41 (46)	284 (43)	39 (53)	13 (31)	14 (50)	625 (45)	1702 (42)
Current	5 (14)	4 (19)	5 (19)	3 (4)	21 (7)	20 (22)	134 (20)	4 (5)	15 (36)	6 (21)	218 (16)	573 (14)

*At index date of criteria fulfilment.
ANCA, antineutrophil cytoplasmic antibody; APS, antiphospholipid syndrome; BMI, body mass index,; EHR, electronic health record; kg, kilograms; m, metres; PMR, polymyalgia rheumatica; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus.

Table 2 Association between preceding sinusitis and incident rheumatic disease

	Any sinusitis, n (%)		Adjusted OR* for rheumatic disease by exposure		
Rheumatic disease	**Cases**	**Controls**	**Any sinusitis (n=5708)**	**Acute sinusitis (n=5305)**	**Chronic sinusitis (n=5263)**
Any rheumatic disease	195 (14)	437 (10)	**1.4 (1.2 to 1.7)**	**1.4 (1.1 to 1.7)**	**1.5 (1.3 to 1.9)**
Rheumatoid arthritis	97 (14)	235 (11)	1.3 (1.0 to 1.6)	1.2 (0.9 to 1.7)	1.3 (0.9 to 1.8)
Seropositive	61 (13)	160 (12)	1.2 (0.8 to 1.6)	1.0 (0.7 to 1.5)	1.3 (0.8 to 1.9)
Seronegative	36 (15)	75 (11)	1.5 (1.0 to 2.3)	**1.8 (1.1 to 3.1)**	1.3 (0.7 to 2.3)
Spondyloarthritis	17 (15)	37 (11)	1.3 (0.7 to 2.5)	1.5 (0.7 to 3.0)	1.3 (0.6 to 2.9)
Ankylosing spondylitis†	5 (23)	8 (12)	2.4 (0.6 to 9.2)	2.2 (0.5 to 9.0)	8.6 (0.9 to 79)
Psoriatic arthritis	12 (13)	29 (11)	1.1 (0.5 to 2.3)	1.3 (0.6 to 3.0)	0.8 (0.3 to 2.1)
Systemic autoimmune rheumatic disease	37 (18)	58 (10)	**2.2 (1.4 to 3.5)**	**1.9 (1.0 to 3.5)**	**2.6 (1.5 to 4.5)**
Antiphospholipid syndrome†	7 (27)	3 (4)	**7.0 (1.8 to 27)**	N/A	**6.0 (1.5 to 24)**
Sjögren's syndrome	16 (22)	24 (11)	**2.4 (1.1 to 5.3)**	2.4 (1.0 to 5.9)	2.5 (0.9 to 6.7)
Systemic lupus erythematosus†	3 (7)	17 (13)	0.5 (0.1 to 1.8)	N/A	0.9 (0.2 to 3.7)
Systemic sclerosis†	4 (14)	8 (9)	1.7 (0.4 to 6.8)	1.5 (0.3 to 7.2)	1.7 (0.4 to 7.9)
Vasculitis	44 (10)	107 (8)	1.3 (0.9 to 1.9)	1.3 (0.8 to 2.1)	1.4 (0.9 to 2.2)
ANCA-associated vasculitis†	6 (16)	13 (11)	1.5 (0.5 to 4.4)	1.6 (0.4 to 5.9)	2.1 (0.6 to 6.9)
Giant cell arteritis	9 (11)	21 (9)	1.3 (0.5 to 3.3)	1.3 (0.4 to 4.5)	1.3 (0.4 to 4.5)
Polymyalgia rheumatica	29 (9)	73 (8)	1.2 (0.8 to 1.9)	1.2 (0.7 to 2.1)	1.3 (0.8 to 2.3)

*Reference group was individuals with no sinusitis codes prior to index date. Adjusting for age, sex, electronic health record history, race and ethnicity, body mass index, smoking status. Bold values were statistically significant.
†Unadjusted conditional logistic regression due to small sample size.
ANCA, antineutrophil cytoplasmic antibody; N/A, not applicable due to insufficient exposures.

smokers. These findings provide novel insights related to the pathogenesis of rheumatic diseases.

The first key and novel finding from this study was that sinusitis was associated with multiple incident rheumatic diseases including APS, Sjögren's disease and seronegative RA. The association was strongest for systemic autoimmune rheumatic diseases including APS and Sjögren's disease, with history of sinusitis conferring over twofold

Table 3 Association between any preceding sinusitis and incident rheumatic disease, stratified by time of first sinusitis exposure

	Adjusted* OR (95% CI), years before index		
Rheumatic disease	**>1 to 5 years (n=189)**	**>5 to 10 years (n=216)**	**>10 years (n=227)**
Any rheumatic disease	**1.4 (1.0 to 1.9)**	**1.7 (1.3 to 2.3)**	1.2 (0.8 to 1.6)
Rheumatoid arthritis	**1.6 (1.1 to 2.5)**	1.2 (0.8 to 1.9)	1.1 (0.7 to 1.6)
Seropositive	1.4 (0.8 to 2.5)	1.1 (0.7 to 1.9)	1.0 (0.6 to 1.7)
Seronegative	2.0 (1.0 to 4.1)	1.3 (0.6 to 2.9)	1.2 (0.6 to 2.5)
Spondyloarthritis	1.0 (0.3 to 3.1)	2.2 (0.8 to 6.2)	1.2 (0.4 to 3.2)
Ankylosing spondylitis†	1.3 (0.1 to 13)	2.4 (0.3 to 18)	4.5 (0.4 to 55)
Psoriatic arthritis	0.9 (0.2 to 3.4)	2.2 (0.6 to 7.5)	0.8 (0.2 to 2.6)
Systemic autoimmune rheumatic disease	2.0 (0.9 to 4.3)	**2.7 (1.3 to 5.7)**	1.9 (0.9 to 4.2)
Antiphospholipid syndrome†	**6.0 (1.1 to 33)**	N/A	3.0 (0.2 to 48)
Sjögren's syndrome	2.0 (0.5 to 7.6)	**3.2 (1.1 to 9.5)**	2.0 (0.6 to 6.9)
Systemic lupus erythematosus†	0.5 (0.1 to 4.1)	0.7 (0.1 to 5.9)	0.4 (0.1 to 3.4)
Systemic sclerosis†	N/A	1.3 (0.1 to 14)	7.4 (0.7 to 74)
Vasculitis	0.8 (0.4 to 1.7)	**2.0 (1.2 to 3.4)**	0.9 (0.4 to 1.9)
ANCA-associated vasculitis†	0.4 (0.0 to 4.4)	3.5 (0.8 to 16)	1.1 (0.1 to 11)
Giant cell arteritis	2.0 (0.5 to 7.8)	1.2 (0.3 to 4.5)	0.4 (0.0 to 5.4)
Polymyalgia rheumatica	0.6 (0.2 to 1.7)	**2.0 (1.0 to 3.8)**	1.0 (0.4 to 2.2)

*Reference group was individuals with no sinusitis codes prior to index date. Adjusting for age, sex, electronic health record history, race and ethnicity, body mass index, smoking status. Bold values were statistically significant.
†Unadjusted conditional logistic regression due to small sample size.
ANCA, antineutrophil cytoplasmic antibody; N/A, not applicable due to insufficient exposures.

Table 4 Association between any preceding sinusitis and incident rheumatic disease by number of sinusitis diagnosis codes

Rheumatic disease	Adjusted*OR for disease (95% CI)			
	1–3 codes (n=275)	4–6 codes (n=190)	7+ codes (n=167)	P value
Any rheumatic disease	1.2 (0.9 to 1.6)	**1.4 (1.0 to 1.9)**	**1.7 (1.2 to 2.4)**	**0.001**
Rheumatoid arthritis	1.1 (0.8 to 1.6)	1.4 (0.9 to 2.1)	1.4 (0.9 to 2.2)	0.27
Seropositive	1.1 (0.7 to 1.8)	1.1 (0.6 to 1.9)	1.4 (0.8 to 2.4)	0.77
Seronegative	1.1 (0.5 to 2.2)	2.0 (1.0 to 4.2)	1.6 (0.7 to 3.3)	0.20
Spondyloarthritis	2.1 (0.8 to 5.0)	0.6 (0.1 to 3.5)	1.0 (0.3 to 3.0)	0.42
Ankylosing spondylitis†	3.0 (0.4 to 26)	1.0 (0.1 to 9.3)	7.2 (0.6 to 86)	0.80
Psoriatic arthritis	1.8 (0.7 to 4.9)	0.6 (0.0 to 8.9)	0.6 (0.2 to 2.2)	0.53
Systemic autoimmune rheumatic disease	1.7 (0.9 to 3.2)	2.0 (1.0 to 4.2)	**4.8 (1.7 to 13)**	**0.004**
Antiphospholipid syndrome†	**21 (3.0 to 171)**	N/A	N/A	N/A
Sjögren's syndrome	0.9 (0.2 to 3.3)	3.1 (1.0 to 9.4)	**8.7 (1.4 to 52)**	**0.02**
Systemic lupus erythematosus†	0.6 (0.1 to 2.9)	0.5 (0.1 to 4.0)	N/A	0.97
Systemic sclerosis†	1.2 (0.1 to 12)	0.9 (0.1 to 8.3)	6.1 (0.5 to 69)	0.87
Vasculitis	0.9 (0.5 to 1.7)	1.2 (0.7 to 2.3)	**2.1 (1.1 to 4.2)**	0.18
ANCA-associated vasculitis†	1.0 (0.2 to 5.2)	0.6 (0.1 to 5.6)	8.5 (0.9 to 83)	0.74
Giant cell arteritis	0.6 (0.1 to 2.7)	2.9 (0.7 to 13)	1.5 (0.1 to 16)	0.47
Polymyalgia rheumatica	1.0 (0.5 to 2.0)	1.0 (0.5 to 2.3)	1.8 (0.8 to 4.0)	0.53

*Reference group was individuals with no sinusitis codes prior to index date. Adjusting for age, sex, electronic health record history, race and ethnicity, body mass index, smoking status. Bold values were statistically significant. P values provided are 2 df p values from these models.
†Unadjusted conditional logistic regression due to small sample size.
ANCA, antineutrophil cytoplasmic antibody; N/A, not applicable due to insufficient exposures.

increased risk of these diseases. Previous literature supports these associations. For example, prior studies showed an association between preceding sinusitis and ANCA-associated vasculitis[16] and RA.[14 15] In addition, preceding infections are associated with both GCA[18 19] and Sjögren's disease.[20] Furthermore, patients with rheumatic diseases including AS, myositis, RA, Sjögren's and SLE have increased risk of subsequent chronic sinusitis.[39–41] By studying sinusitis at least 1-year prior to incident rheumatic disease, however, this study provides important evidence suggesting a true biological link.

Table 5 Associations between any preceding sinusitis and incident rheumatic disease, stratified by smoking status

Rheumatic disease	Adjusted* OR for disease (95% CI)	
	Never smokers (n=2365)	Ever smokers (n=3118)
Any rheumatic disease	**1.7 (1.3 to 2.3)**	1.2 (0.9 to 1.5)
Rheumatoid arthritis	**1.6 (1.1 to 2.4)**	1.1 (0.8 to 1.5)
Seropositive	**1.6 (1.0 to 2.7)**	0.9 (0.6 to 1.4)
Seronegative	1.5 (0.7 to 2.9)	1.5 (0.8 to 2.8)
Spondyloarthritis	1.3 (0.5 to 3.7)	1.4 (0.6 to 3.1)
Ankylosing spondylitis†	2.2 (0.4 to 13)	2.6 (0.3 to 20)
Psoriatic arthritis	0.9 (0.2 to 3.4)	1.3 (0.5 to 3.1)
Systemic autoimmune rheumatic disease	**2.3 (1.2 to 4.3)**	**2.1 (1.1 to 4.1)**
Antiphospholipid syndrome†	N/A	1.7 (0.3,11)
Sjögren's syndrome	2.1 (0.7 to 6.1)	**2.9 (1.0 to 8.2)**
Systemic lupus erythematosus†	0.7 (0.1 to 3.9)	0.3 (0.0 to 2.6)
Systemic sclerosis†	3.4 (0.5 to 23)	1.3 (0.2 to 8.1)
Vasculitis	**1.9 (1.1 to 3.2)**	0.9 (0.5 to 1.5)
ANCA-associated vasculitis†	2.3 (0.4 to 14)	1.1 (0.3 to 4.1)
Giant cell arteritis	1.2 (0.4 to 4.1)	1.4 (0.3 to 5.6)
Polymyalgia rheumatica	**2.0 (1.1 to 3.9)**	0.7 (0.4 to 1.4)

*Reference group was individuals with no sinusitis codes prior to index date. Adjusting for age, sex, electronic health record history, race and ethnicity, body mass index, smoking status. Bold values were statistically significant.
†Unadjusted conditional logistic regression due to small sample size.

One possible explanation for the observed association between sinusitis and rheumatic disease could be a shared immune defect that simultaneously predisposes to mucosal infection and breakdown of tolerance. For example, individuals with RA also have increased risk for allergic diseases.[42] Similarly, sinusitis could represent an early manifestation of disease, as is already recognised for ANCA-associated vasculitis.[16] However, the fact that the association was strongest in the 5–10 years before disease onset points away from these explanations. Unmeasured confounding such as from antibiotic exposure might also explain the association. However, the Nurses' Health Study showed no association between antibiotic use and RA.[43] In fact, certain antibiotics ameliorate rather than exacerbate APS,[44] AS[45] and RA[46] symptoms. A third explanation, therefore, could be that pathogenic organisms such as those involved in sinusitis play a causal role in disease. Indeed, both *Staphylococcus* and more recently *Corynebacterium* were implicated in pathogenesis of ANCA-associated vasculitis,[47] whereas *Ruminococcus gnavus* was associated with lupus nephritis,[48] RA[49] and spondyloarthritis.[49] Furthermore, sinusitis is associated with accelerated atherosclerosis, further supporting its potential inflammatory effects.[50] Therefore, future studies should replicate the observed association between sinusitis and

rheumatic diseases, search for additional causative organisms and determine whether preventing or treating sinusitis can prevent and/or treat rheumatic diseases.

A second key and novel finding from this study was that the association was strongest for sinusitis occurring 5–10 years before disease onset. For example, sinusitis occurring 5–10 years beforehand was associated with around threefold odds of Sjögren's disease and ANCA-associated vasculitis (though the latter was not statistically significant). This finding fits with our hypothesis as well as a prior study of sinusitis and incident RA.[15] Such timing argues against reverse causation (eg, Sjögren's-related immune defects or dryness causing sinusitis) since sinusitis in the 1–5 years leading up to disease onset was less associated with these diseases. In addition, rheumatic disease autoantibodies including antinuclear antigen, ANCA, anti-CCP, RF and anti-Sjögren Syndrome (SS)A/B become detectable in nearly the same window, approximately 3–8 years before disease onset.[51–54] On the other hand, sinusitis showed an elevated association with RA and APS in the 1–5 years window before disease. While this could reflect reverse causation, it could also point toward an infectious trigger. Indeed, infections are associated with RF[55] and antiphospholipid antibodies themselves and believed to play a causal role in APS based on evidence for molecular mimicry between APS-related peptides and common pathogens.[44]

Another finding that points toward a true association was that increasing burden of sinusitis, as measured by number of codes, showed a dose-response association with disease. Prior studies of infections in Sjögren's disease[20] and GCA[19] also showed a dose-response association. In our study, the dose-response association was present for all diseases where a significant overall association was observed, including any rheumatic disease, systemic autoimmune rheumatic diseases, Sjögren's disease and vasculitis. In addition, the dose-response association for acute sinusitis in seronegative RA suggests that the lack of association between sinusitis and overall RA in this study could have resulted from rule out codes, which would bias results towards the null. Other reasons, however, could include better capture of data for controls given the population-based design, different disease biology in different geographical regions or the smaller proportion of never smokers in this study (37%) compared with our previous study (50%).[14]

Indeed, a fourth key result from this study was that the association between sinusitis and incident rheumatic diseases was strongest among never smokers. One explanation for this finding could be chance alone, as the interaction p values were not significant. Another explanation to consider could be the 'risk factor paradox,' also called index event bias. Index event bias occurs from conditioning on the presence of an event (eg, RA), which induces an artificial negative association between its risk factors (eg, smoking and sinusitis).[56] A biological explanation, however, could be that both smoking and sinusitis provide a similar and therefore redundant inflammatory trigger for disease. If true, the strong association between sinusitis and rheumatic disease among never smokers will become more relevant as smoking rates continue to decline.

Strengths of this study include its population-based design, manual verification of rheumatic diseases and their time of onset using validated classification criteria and relatively long duration of EHR history. However, there are several important limitations to consider. First, the findings may not generalise outside this single geographical region, especially since this population is predominately white and rheumatic disease outcomes are known to vary by race and ethnicity.[57] Second, results also may not generalise to all severities of sinusitis, as sinusitis that reaches medical care is more likely to be severe. Third, limited sample size limited power and precluded adjusted analysis for several rheumatic diseases of interest such as ANCA-associated vasculitis and APS. For example, sinusitis was not associated with GCA or SLE as we initially hypothesised, though the sample size was small and therefore CIs were wide for both. Fourth, some misclassification of sinusitis exposure is possible since sinusitis exposures were based on billing codes. However, sinusitis codes had 96% PPV by physician diagnosis in our study, and a 92% PPV in our previous study.[14] Furthermore, misclassification of sinusitis exposure would bias results towards null. Fifth, reverse causation is possible where the rheumatic diseases themselves increase the risk of sinusitis. For example, disease-related symptoms begin a median of 7–24 days before RA criteria fulfilment,[58] 1.1 months before GCA criteria fulfilment[27] and 29 months before SLE criteria fulfilment[59] in our cohorts. To minimise this risk, we required sinusitis exposure to occur at least 1 year before disease onset. Sixth, unmeasured confounding is possible such as drug use (antibiotics, aspirin, non-steroidal anti-inflammatory drugs, antihistamines), atopy, periodontitis[60] and healthcare utilisation. Finally, we performed multiple comparisons in this study, though each disease was prespecified in our protocol.

In summary, this study found that preceding history of sinusitis was associated with increased incidence of rheumatic diseases including APS, Sjögren's disease and seronegative RA. These associations were strongest in the 5–10 years before disease onset, for the highest number of sinusitis codes and among never smokers. Overall, these findings point towards a role for sinus inflammation in the presentation, and possibly pathogenesis, of rheumatic disease.

Correction notice This article has been corrected since it was first published online. The polymyalgia rheumatica (PMR) cohort inadvertently included controls from a previous analysis. Eliminating those controls reduced the sample size of the PMR cohort from 610 to 308. This impacted the results for the PMR cohort as well as the categories PMR contributed to (ie, vasculitis and anyrheumatic disease). This has now been rectified in-text.

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