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## Increased risk of osteoarthritis in patients with atopic disease

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## ABSTRACT

**Objectives** To determine the incidence of osteoarthritis (OA) in patients with atopic disease compared with matched non-exposed patients.

**Methods** We conducted a retrospective cohort study with propensity score matching using claims data from Optum's de-identified Clinformatics Data Mart (CDM) (January 2003 to June 2019) and electronic health record data from the Stanford Research Repository (STARR) (January 2010 to December 2020). We included adult patients without pre-existing OA or inflammatory arthritis who were exposed to atopic disease or who were non-exposed. The primary outcome was the development of incident OA.

**Results** In Optum CDM, we identified 117 346 exposed patients with asthma or atopic dermatitis (mean age 52 years; 60% female) and 1 247 196 non-exposed patients (mean age 50 years; 48% female). After propensity score matching (n=1 09 899 per group), OA incidence was higher in patients with asthma or atopic dermatitis (26.9 per 1000 person-years) compared with non-exposed patients (19.1 per 1000 person-years), with an adjusted odds ratio (aOR) of 1.58 (95% CI 1.55 to 1.62) for developing OA. This effect was even more pronounced in patients with both asthma and atopic dermatitis compared with non-exposed patients (aOR=2.15; 95% CI 1.93 to 2.39) and in patients with asthma compared with patients with chronic obstructive pulmonary disease (aOR=1.83; 95% CI 1.73 to 1.95). We replicated our results in an independent dataset (STARR), which provided the added richness of body mass index data. The aOR of developing OA in patients with asthma or atopic dermatitis versus non-exposed patients in STARR was 1.42 (95% CI 1.36 to 1.48).

**Conclusions** This study demonstrates an increased incidence of OA in patients with atopic disease. Future interventional studies may consider targeting allergic pathways for the prevention or treatment of OA.

## INTRODUCTION

Osteoarthritis (OA) is the most common form of arthritis, with a lifetime risk of developing symptomatic knee OA as high as 44.7%.<sup>1,2</sup> Osteoarthritis is associated with considerable morbidity—it is one of the major contributors to the global years lived with disability and the principal cause of lower extremity disability in older adults.<sup>3</sup> Despite the high prevalence, substantial economic burden and debilitating impact of OA, the current therapeutic armamentarium is limited and focuses on symptom management. To date, there are no effective

## WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Osteoarthritis (OA) is a common chronic disabling disease for which few effective treatments exist. Mounting evidence suggests that mast cell activation and allergic pathways may play key roles in OA pathogenesis. If so, OA occurrence may be increased in patients with atopic diseases; however, this currently remains unknown.

## WHAT THIS STUDY ADDS

⇒ In this propensity score matched study using administrative health claims data, we found a significantly increased incidence of OA in patients with asthma or atopic dermatitis or the combination of both asthma and atopic dermatitis. These results were confirmed in an academic institutional cohort.

## HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This study demonstrates an association between atopic disease and the development of OA; patients may benefit from the use of treatments that inhibit mast cells and allergic cytokines to treat or prevent OA.

disease-modifying drugs that halt, slow or reverse the progression of OA.<sup>4</sup>

Accumulating evidence implicates chronic, low-grade inflammation as a key driver of OA pathogenesis.<sup>5</sup> We previously demonstrated increased activation and degranulation of mast cells in human OA synovium,<sup>6</sup> and others demonstrated a correlation between synovial mast cell numbers and synovitis scores.<sup>7</sup> In addition, we reported that IgE-mediated activation of mast cells and the mast cell mediator tryptase play key roles in driving the pathogenesis of OA in mice.<sup>6</sup> Single nucleotide polymorphisms in interleukin 4 (IL-4)-associated genes, which are associated with type 2 inflammation and atopic disease, are also associated with OA.<sup>8–11</sup> Together, these findings suggest that atopic disease might predispose or contribute to the development of OA in humans.

The aim of this study was to investigate whether patients with atopic disease have an increased risk of developing OA. To address this question, we used a nationwide insurance claims database and electronic health records from a large academic

institution to determine the risk of developing OA in patients with asthma and/or atopic dermatitis.

## METHODS

This study adhered to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines for cohort studies and was approved by the Stanford University institutional review board (IRB-57463). There was no patient or public involvement in this study.

### Data source

We used Optum's de-identified Clinformatics Data Mart Database (CDM), a database derived from large, adjudicated claims data, from January 1, 2003 to June 30, 2019, and electronic health records from the Stanford Research Repository (STARR) from January 1, 2010 to December 31, 2020.<sup>12</sup>

### Study populations

#### Optum CDM cohort

The Optum CDM study population included individuals aged 18 years or older with at least 7 years of continuous enrolment in Optum CDM. Patients were excluded if they had a diagnosis of OA or atopic disease in the first 2 years of enrolment (defined by one or more International Classification of Disease (ICD) code 9 or 10 for OA or atopic disease) or any history of inflammatory arthritis based on one or more ICD-9 or ICD-10 code (online supplemental table 1). The exclusion of patients with prior OA or atopic disease was done to ensure the order of events: that patients did not have pre-existing OA, that patients in the exposed group then developed incident atopic disease, whereas patients in the non-exposed group did not develop atopic disease, and that the outcome of incident OA could then be assessed in both groups. It was necessary to include only patients who developed atopic disease after 2 years of enrolment, as including patients with atopic disease in their first year of enrolment would not allow for a lookback period of 2 years before this exposure, which was needed to exclude pre-existing OA and to ensure that we captured confounder information as comprehensively as possible.

The exposed group included patients with a diagnosis of incident atopic disease, specifically asthma and/or atopic dermatitis. Asthma was defined as two or more ICD-9 or ICD-10 codes for asthma separated by 7 days or more, and a prescription for an inhaler after the earliest ICD diagnosis date.<sup>13–16</sup> Atopic dermatitis was defined as two or more ICD-9 or ICD-10 codes for atopic dermatitis separated by 7 days or more, and in addition, at least two visits to a dermatologist and at least one prescription for an emollient, topical corticosteroid or topical calcineurin inhibitor.<sup>17</sup>

The non-asthma/non-atopic dermatitis group (called the non-exposed group) was defined as patients without an ICD-9 or ICD-10 code for asthma or atopic dermatitis. Patients with only one ICD-9 or ICD-10 code for asthma or atopic dermatitis, and therefore not meeting the criteria for exposed or non-exposed were excluded from the analysis. For the secondary analysis in the Optum CDM cohort, patients with chronic obstructive pulmonary disease (COPD) were compared with patients with asthma. COPD was chosen as a comparator given the similarities with asthma—both are pulmonary diseases that are associated with increased healthcare use—however, COPD is not mediated by allergic pathology. Patients with COPD were defined as having two or more ICD-9 or ICD-10 codes for COPD separated by 7 days or more and a prescription for an inhaler

( $\beta$ -adrenergic agent, anticholinergic or inhaled glucocorticoid) after the earliest ICD diagnosis date for COPD.

#### STARR cohort

The study population for the STARR cohort included individuals from the Stanford Research Repository, aged 18 years or older, with at least 5 years continuous enrolment; 5 years of continuous follow-up rather than 7 years was chosen for this cohort in order to maximise the sample size in this smaller dataset. Patients were excluded if they had a diagnosis of OA or atopic disease in the first 2 years of enrolment (defined by one or more ICD-9 or ICD-10 code for OA or atopic disease) or any history of inflammatory arthritis based on one or more ICD-9 or ICD-10 code (online supplemental table 1). The same definitions as for the Optum CDM cohort for exposed and non-exposed were used.

For both cohorts, we extracted data on age, sex, race/ethnicity, duration of follow-up and outpatient visit frequency. We applied R package 'comorbidity' to calculate the Charlson Comorbidity Score, using all ICD codes within the 5-year window around the index date for each patient.<sup>18,19</sup> For the exposed group, the duration of follow-up started from the diagnosis date of atopic disease. For the non-exposed group, in order to deal with immortal time bias (time during which the patient cannot experience the outcome), we individually matched non-exposed patients with exposed patients using prescription time-distribution matching.<sup>20</sup> This method generates an index date for the non-exposed patients by randomly sampling with replacement from the empirical distribution of the duration of immortal time from the exposed group. Thus, the index date for exposed patients was the date of diagnosis of atopic disease and the index date for non-exposed patients was the eligibility start date plus a randomly assigned duration of immortal time. This method helps to balance immortal time between the exposed and non-exposed groups.

### Outcome ascertainment

The primary outcome was the development of OA, which was defined as two or more ICD-9 or ICD-10 codes for OA separated by 7 days or more. The use of two or more codes for OA has a positive predictive value of 0.85, sensitivity of 0.25, and specificity of 0.91 for the presence of knee, hand or hip OA,<sup>21,22</sup> using the American College of Rheumatology classification criteria for OA as the standard,<sup>23</sup> and these criteria have been used in previous OA studies.<sup>24–26</sup> As a secondary outcome, we also analysed OA subtypes, including OA of the knee, hip and hands. Patients were followed up until the eligibility end date of the last insurance plan (ie, if there were gaps in coverage, their follow-up time included only the time they were actually in the dataset, and follow-up time ended when the last period of observation in the dataset ended).

### Statistical analysis

#### Optum CDM cohort

Baseline characteristics of patients with atopic disease and non-exposed patients were described. In the Optum CDM cohort, we conducted 1:1 propensity score matched analyses of (1) patients with asthma or atopic dermatitis versus non-exposed patients, (2) patients with both asthma and atopic dermatitis versus non-exposed patients and (3) patients with asthma versus patients with COPD. For all propensity score matched analyses, patients were matched on age, sex, race/ethnicity, education level, Charlson Comorbidity Score, duration of follow-up and outpatient visit frequency.<sup>18</sup> Subjects who could not be matched

were excluded. Standardised mean differences (SMDs) were calculated using the 'stddiff' package in R.<sup>27</sup> Standardised mean differences were used to describe the magnitude of difference in characteristics between cohorts. An SMD  $\geq 0.20$  was interpreted as meaningful. The magnitude of effect was considered small if SMD was  $\geq 0.20$  to  $< 0.50$ , medium if SMD was  $\geq 0.50$  to  $< 0.80$  and large if SMD was  $\geq 0.80$ . Logistic regression was used to estimate the propensity score. Complete case analysis was performed, as the level of missing variables was low ( $< 1\%$  for all continuous covariates). All missing categorical variables were coded as 'unknown.'

For the propensity score matched Optum CDM cohort, the relationship between atopic disease and the development of OA was evaluated using logistic regression. In our multivariable propensity score matched model, we also adjusted for age, sex, race/ethnicity, Charlson Comorbidity Score, education, duration of follow-up and frequency of outpatient visits. Raw incidence rates with 95% confidence intervals were calculated for each comparison group using the R package 'epiR', both before and after propensity score matching. Calculating the raw incidence rate using propensity score matched cohorts provided adjusted incidence rates (adjusted for all variables used in matching).

### STARR cohort

To test the robustness of our results, we performed a second analysis using the STARR dataset, which included information on body mass index (BMI). For this analysis, we did not use propensity score matching owing to the smaller sample sizes. In order to assess the relationship between atopic disease and the development of OA, we calculated raw incidence rates as above and performed multivariable logistic regression, adjusting

for age, sex, race/ethnicity, BMI, Charlson Comorbidity Score, duration of follow-up and frequency of outpatient visits. BMI was extracted at the index date and was present for roughly 97% of patients (otherwise listed as 'unknown' if missing).

For both cohorts, all statistical analyses were conducted using R software, version 4.0.<sup>28</sup> All 95% CIs and p values were based on two-sided hypothesis tests, where a p value of  $< 0.05$  was considered statistically significant.

## RESULTS

### Optum CDM cohort before propensity score matching

In the Optum CDM cohort, there were a total of 1 364 542 patients meeting inclusion and exclusion criteria, including 117 346 exposed patients with asthma or atopic dermatitis and 1 247 196 non-exposed patients (online supplemental figure 1). Before propensity score matching, for patients with asthma or atopic dermatitis compared with non-exposed patients, the mean age was 52 vs 50 years, the percentage female was 60% vs 48%, the mean Charlson Comorbidity Score was 1.6 vs 0.9, and the mean number of outpatient visits per year was 6.7 vs 6.0 (table 1).

Before propensity score matching, the incidence rate of developing OA per 1000 person-years was 27.1 (95% CI 26.8 to 27.4) for patients with asthma or atopic dermatitis, 34.8 (95% CI 33.0 to 36.7) for patients with both asthma and atopic dermatitis, and 14.2 (95% CI 14.1 to 14.3) for non-exposed patients over 5 years or more of follow-up (table 2). Compared with non-exposed patients, after adjusting for age, sex, race/ethnicity, Charlson Comorbidity Score, education, duration of follow-up and frequency of outpatient visits, the aOR of developing OA in patients with asthma or atopic dermatitis was 1.76 (95% CI

**Table 1** Baseline characteristics of patients in the Optum Clinformatics Data Mart cohort

Characteristics	Total cohort (n=1 364 542)	Non-exposed (n=1 247 196)	Asthma or atopic dermatitis (n=117 346)	Asthma (n=35 097)	Atopic dermatitis (n=77 854)	Both asthma and atopic dermatitis (n=4395)
Age in years, mean (SD)	50.4 (15.7)	50.2 (15.7)	52.0 (15.4)	53.3 (15.9)	51.4 (15.2)	52.7 (15.4)
Gender, n (%)						
Female	664 426 (48.7)	593 492 (47.6)	70 934 (60.4)	21 578 (61.5)	46 401 (59.6)	2955 (67.2)
Male	699 939 (51.3)	653 538 (52.4)	46 401 (39.5)	13 519 (38.5)	31 442 (40.4)	1440 (32.8)
Unknown	177 (0.0)	166 (0.0)	11 (0.0)	0 (0.0)	11 (0.0)	0 (0.0)
Race, n (%)						
White	980 962 (71.9)	892 755 (71.6)	88 207 (75.2)	25 219 (71.9)	59 637 (76.6)	3351 (76.2)
Black	119 572 (8.8)	110 452 (8.9)	9120 (7.8)	3035 (8.6)	5743 (7.4)	342 (7.8)
Asian	67 302 (4.9)	61 867 (5.0)	5435 (4.6)	1432 (4.1)	3839 (4.9)	164 (3.7)
Hispanic	161 878 (11.9)	150 297 (12.1)	11 581 (9.9)	4678 (13.3)	6473 (8.3)	430 (9.8)
Unknown	34 828 (2.6)	31 825 (2.6)	3003 (2.6)	733 (2.1)	2162 (2.8)	108 (2.5)
Education, n (%)						
Less than 12th grade	8222 (0.6)	7791 (0.6)	431 (0.4)	236 (0.7)	172 (0.2)	23 (0.5)
High school diploma	301 911 (22.1)	281 546 (22.6)	20 365 (17.4)	8056 (23.0)	11 561 (14.8)	748 (17.0)
Less than bachelor's degree	752 617 (55.2)	688 848 (55.2)	63 769 (54.3)	19 989 (57.0)	41 364 (53.1)	2416 (55.0)
Bachelor's degree or higher	297 270 (21.8)	264 789 (21.2)	32 481 (27.7)	6727 (19.2)	24 558 (31.5)	1196 (27.2)
Unknown	4522 (0.3)	4222 (0.3)	300 (0.3)	89 (0.3)	199 (0.3)	12 (0.3)
Charlson Comorbidity Score, n (%)						
0–1	1 085 288 (79.5)	1 006 765 (80.7)	78 523 (66.9)	19 122 (54.5)	56 874 (73.1)	2527 (57.5)
2–3	169 536 (12.4)	146 518 (11.7)	23 018 (19.6)	9089 (25.9)	12 829 (16.5)	1100 (25.0)
4–5	57 652 (4.2)	49 315 (4.0)	8337 (7.1)	3693 (10.5)	4199 (5.4)	445 (10.1)
$\geq 6$	52 066 (3.8)	44 598 (3.6)	7468 (6.4)	3193 (9.1)	3952 (5.1)	323 (7.3)
Charlson Comorbidity, mean (SD)	0.94 (1.83)	0.88 (1.79)	1.59 (2.13)	2.34 (2.16)	1.23 (2.03)	2.04 (2.11)
Years of follow-up, mean (SD)	7.7 (2.4)	7.7 (2.4)	8.1 (2.3)	8.2 (2.3)	8.0 (2.3)	9.2 (2.5)
Yearly outpatient visits, mean (SD)	6.1 (20.4)	6.0 (21.1)	6.7 (8.9)	6.7 (7.0)	6.6 (9.8)	8.0 (4.9)

**Table 2** Incidence and odds ratio of developing osteoarthritis (OA) in exposed patients with atopic disease versus non-exposed patients in Optum Clinformatics Data Mart.

	Optum CDM cohort				
	Asthma only (n=35 097)	Atopic dermatitis only (n=77 854)	Asthma or atopic dermatitis (n=117 346)	Both asthma and atopic dermatitis (n=4395)	Non-exposed (n=1 247 196)
Incident OA, n (%)	8674 (24.7)	15 738 (20.2)	25 817 (22.0)	1405 (32.0)	136 494 (10.9)
Person-years	285 947	625 999	952 284	40 339	9 609 283
IR (95% CI)	30.3 (29.7 to 31.0)	25.1 (24.7 to 25.5)	27.1 (26.8 to 27.4)	34.8 (33.0 to 36.7)	14.2 (14.1 to 14.3)
aOR (95% CI)	1.90 (1.84 to 1.95)	1.66 (1.62 to 1.69)	1.76 (1.73 to 1.79)	2.41 (2.25 to 2.59)	1.0

aOR, adjusted odds ratio (adjusted for age, sex, race/ethnicity, Charlson Comorbidity Score, education, duration of follow-up and frequency of outpatient visits); IR, incidence rate per 1000 person-years; OA, osteoarthritis.

1.73 to 1.79,  $p < 0.001$ ), and it was 2.41 (95% CI 2.25 to 2.59,  $p < 0.001$ ) in patients with both asthma and atopic dermatitis (table 2).

### Optum CDM propensity score matched cohorts

#### Asthma or atopic dermatitis versus non-exposed patients

Patients with asthma or atopic dermatitis (n=109 899) were propensity score matched with non-exposed patients (n=109 899). The mean age in both cohorts was 52 years, with 59% female, a mean Charlson Comorbidity Score of 1.6, a mean number of outpatient visits per year of 7 and a mean follow-up time of 8 years (online supplemental table 2). The incidence rate of OA was 26.9 (95% CI 26.6 to 27.3) per 1000 person-years for patients with asthma or atopic dermatitis compared with 19.1 (95% CI 18.9 to 19.4) per 1000 person-years for non-exposed patients, with an aOR of developing OA in patients with asthma or atopic dermatitis compared with non-exposed patients of 1.58 (95% CI 1.55 to 1.62,  $p < 0.001$ ) (figure 1). For knee, hip and hand OA subtypes, the incidence rates of OA per 1000 person-years in patients with asthma or atopic dermatitis compared with non-exposed patients were 10.9 vs 7.5, 3.3 vs 2.3 and 2.3 vs 1.3 (online supplemental table 3).

#### Both asthma and atopic dermatitis versus non-exposed patients

After propensity score matching, patients with both asthma and atopic dermatitis (n=4325) and non-exposed patients (n=4325) were similar in age (53 years), sex (67% female), with a mean Charlson Comorbidity Score of 2, a mean number of outpatient visits per year of 8 and a mean follow-up time of 9 years (online supplemental table 4). The incidence rate of OA was 35.0 (95% CI 33.2 to 36.9) per 1000 person-years for patients with both asthma and atopic dermatitis compared with 21.5 (95% CI 20.0 to 22.9) per 1000 person-years for non-exposed patients. The aOR of developing OA in patients with both asthma and atopic dermatitis compared with non-exposed patients was 2.15 (95% CI 1.93 to 2.39,  $p < 0.001$ ) (figure 1). For knee, hip and hand OA subtypes, the incidence rates of OA per 1000 person-years in

patients with both asthma and atopic dermatitis compared with non-exposed patients were 15.3 vs 9.1, 4.2 vs 3.0 and 3.9 vs 2.1 (online supplemental table 3).

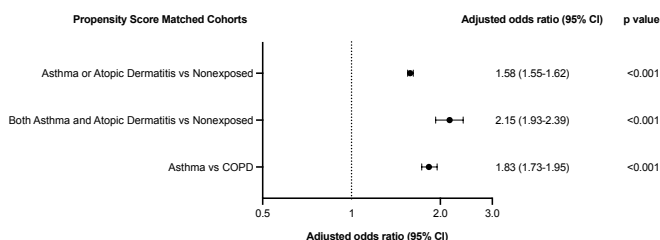
#### Asthma versus patients with COPD

As a secondary analysis using the Optum CDM dataset, patients with asthma only (n=11 820) were compared with patients with COPD and no history of atopic disease (n=11 820). After propensity score matching, in both groups the average age was 65 years, 53% of patients were female, the mean Charlson Comorbidity Score was 3.4, the mean number of outpatient visits per year was 8, and the mean follow-up time was 8 years (online supplemental table 5). The incidence rate of OA was 41.2 (95% CI 39.9 to 42.5) per 1000 person-years for patients with asthma compared with 27.1 (95% CI 26.1 to 28.2) per 1000 person-years for patients with COPD. The aOR of developing OA was 1.83 (95% CI 1.73 to 1.95,  $p < 0.001$ ) for patients with asthma compared with patients with COPD (figure 1). The higher incidence rate of OA in patients with asthma compared with COPD was seen across knee, hip, and hand OA subtypes (16.3 vs 7.8, 5.1 vs 3.3 and 2.8 vs 1.6 respectively, all per 1000 person-years) (online supplemental table 3).

#### STARR cohort

The STARR cohort comprised 114 427 patients, including 43 728 exposed patients with asthma or atopic dermatitis and 70 699 non-exposed patients without atopic disease (online supplemental figure 2). Compared with non-exposed patients, those with asthma or atopic dermatitis were younger (mean age 51 vs 53 years), were more likely to be female (64% vs 61%), had a higher mean Charlson Comorbidity Score (0.9 vs 0.8), had fewer outpatient visits per year (3.9 vs 4.1) and had a slightly higher mean BMI (27.3 vs 27.0) (table 3).

The raw incidence rate for OA per 1000 person-years was 18.6 (95% CI 18.2 to 19.1) for patients with asthma or atopic dermatitis, 17.5 (95% CI 16.6 to 18.5) for patients with both asthma and atopic dermatitis, and 11.4 (95% CI 11.2 to 11.7) for non-exposed patients (table 4). After adjusting for age, sex, race/ethnicity, Charlson Comorbidity Score, duration of follow-up and frequency of outpatient visits, compared with non-exposed patients, the aOR of developing OA in patients with asthma or atopic dermatitis was 1.47 (95% CI 1.42 to 1.53,  $p < 0.001$ ), and the aOR of developing OA in patients with both asthma and atopic dermatitis was 1.25 (95% CI 1.16 to 1.34,  $p < 0.001$ ). After additionally adjusting for BMI, compared with non-exposed patients, the aOR of developing OA in patients with asthma or atopic dermatitis was 1.42 (95% CI 1.36 to 1.48,  $p < 0.001$ ), and the aOR of developing OA in patients with both



**Figure 1** Risk of developing osteoarthritis in Optum Clinformatics Data Mart propensity score matched cohorts. COPD, chronic obstructive pulmonary disease.

**Table 3** Baseline characteristics of patients in the STARR cohort

	Total cohort (n=114 427)	Non-exposed (n=70 699)	Asthma or atopic dermatitis (n=43 728)	Asthma (n=11 101)	Atopic dermatitis (n=23 854)	Both asthma and atopic dermatitis (n=8773)
Age in years, mean (SD)	52.4 (16.2)	53.4 (16.4)	50.8 (15.8)	54.4 (16.6)	49.8 (15.3)	49.1 (15.4)
Gender, n (%)						
Female	70 941 (62.0)	43 071 (60.9)	27 870 (63.7)	7076 (63.7)	14 915 (62.5)	5879 (67.0)
Male	43 486 (38.0)	27 628 (39.1)	15 858 (36.3)	4025 (36.3)	8939 (37.5)	2894 (33.0)
Race, n (%)						
White	67 257 (58.8)	42 209 (59.7)	25 048 (57.3)	7127 (64.2)	12 914 (54.1)	5007 (57.1)
Black	4752 (4.2)	2507 (3.5)	2245 (5.1)	688 (6.2)	1037 (4.3)	520 (5.9)
Asian	19 754 (17.3)	11 557 (16.3)	8197 (18.7)	1268 (11.4)	5373 (22.5)	1556 (17.7)
American Indian/Alaska Native	316 (0.3)	188 (0.3)	128 (0.3)	33 (0.3)	63 (0.3)	32 (0.4)
Native Hawaiian/Pacific Islander	937 (0.8)	503 (0.7)	434 (1.0)	97 (0.9)	226 (0.9)	111 (1.3)
Other	14 862 (13.0)	9345 (13.2)	5517 (12.6)	1512 (13.6)	2852 (12.0)	1153 (13.1)
Unknown	6549 (5.7)	4390 (6.2)	2159 (4.9)	376 (3.4)	1389 (5.8)	394 (4.5)
Ethnicity, n (%)						
Hispanic	10 907 (9.5)	6718 (9.5)	4189 (9.6)	1262 (11.4)	2049 (8.6)	878 (10.0)
Non-Hispanic	93 949 (82.1)	57 778 (81.7)	36 171 (82.7)	9205 (82.9)	19 718 (82.7)	7248 (82.6)
Unknown	9571 (8.4)	6203 (8.8)	3368 (7.7)	634 (5.7)	2087 (8.7)	647 (7.4)
Body mass index, n (%)						
<25 kg/m <sup>2</sup>	46 953 (41.0)	29 221 (41.3)	17 732 (40.6)	3982 (35.9)	10 594 (44.4)	3156 (36.0)
25 to <30 kg/m <sup>2</sup>	37 338 (32.6)	23 153 (32.7)	14 185 (32.4)	3467 (31.2)	7868 (33.0)	2850 (32.5)
≥30 kg/m <sup>2</sup>	26 794 (23.4)	15 448 (21.9)	11 346 (25.9)	3552 (32.0)	5077 (21.3)	2717 (31.0)
Unknown	3342 (2.9)	2877 (4.1)	465 (1.1)	100 (0.9)	315 (1.3)	50 (0.6)
Body mass index, mean (SD)	27.1 (27.5)	27.0 (32.4)	27.3 (17.3)	28.2 (7.1)	26.7 (22.5)	28.1 (6.7)
Charlson Comorbidity Score, n (%)						
0–1	74 030 (64.7)	47 427 (67.1)	26 603 (60.8)	5264 (47.4)	17 616 (73.8)	3723 (42.4)
2–3	29 242 (25.6)	16 688 (23.6)	12 554 (28.7)	3990 (35.9)	4510 (18.9)	4054 (46.2)
4–5	7326 (6.4)	4236 (6.0)	3090 (7.1)	1300 (11.7)	1059 (4.4)	731 (8.3)
≥6	3829 (3.3)	2348 (3.3)	1481 (3.4)	547 (4.9)	669 (2.8)	265 (3.0)
Charlson Comorbidity, mean (SD)	0.86 (1.71)	0.84 (1.70)	0.91 (1.73)	1.30 (2.03)	0.65 (1.55)	1.10 (1.65)
Years of follow-up, mean (SD)	8.1 (1.8)	7.8 (1.7)	8.6 (1.8)	8.4 (1.8)	8.6 (1.8)	8.7 (1.7)
Yearly outpatient visits, mean (SD)	4.0 (18.1)	4.1 (22.2)	3.9 (7.9)	4.0 (10.3)	3.6 (7.7)	4.4 (3.7)

STARR, Stanford Research Repository.

asthma and atopic dermatitis was 1.19 (95% CI 1.11 to 1.28,  $p < 0.001$ ) (table 4).

## DISCUSSION

In our study, compared with non-exposed patients, patients with asthma or atopic dermatitis had a 58% increased risk of developing OA in a nationwide insurance claims dataset and 42% increased risk of developing OA in a large academic institutional dataset, after adjusting for important covariables. Furthermore, in the Optum CDM cohort, after propensity score matching, patients with asthma had an 83% increased risk of developing OA compared with patients with COPD, and patients with both asthma and atopic dermatitis had 115% increased risk of

developing OA compared with non-exposed patients. Notably, the risk of developing OA in patients with atopic disease was attenuated in the STARR cohort after adjusting for BMI compared with the Optum CDM cohort, but overall trends between the two cohorts were consistent. This is the first cohort study to our knowledge to demonstrate an association between atopic disease and the risk of developing OA.

The association between atopic disease and OA support mechanistic studies that implicate a number of allergic pathways in the pathogenesis of OA: (1) activated and degranulating mast cells are statistically increased in the synovium of patients with OA,<sup>6</sup> and there is a non-significant trend between synovial mast cell numbers and OA severity<sup>7</sup>; (2) mast cell activation and the

**Table 4** Incidence and odds ratio of developing osteoarthritis in exposed patients with atopic disease versus non-exposed patients in STARR

	STARR cohort				
	Asthma only (n=11 101)	Atopic dermatitis only (n=23 854)	Asthma or atopic dermatitis (n=43 728)	Both asthma and atopic dermatitis (n=8773)	Non-exposed (n=70 699)
Incident OA, n (%)	1956 (17.6)	3678 (15.4)	6968 (15.9)	1334 (15.2)	6318 (8.9)
Person-years	93 107	204 427	373 725	76 190	552 032
IR (95% CI)	21.0 (20.1 to 21.9)	18.0 (17.4 to 18.6)	18.6 (18.2 to 19.1)	17.5 (16.6 to 18.5)	11.4 (11.2 to 11.7)
aOR (95% CI)	1.48 (1.39 to 1.57)	1.48 (1.41 to 1.55)	1.42 (1.36 to 1.48)	1.19 (1.11 to 1.28)	1.0

aOR, adjusted odds ratio (adjusted for age, sex, race/ethnicity, Charlson comorbidity score, duration of follow-up, and frequency of outpatient visits, and BMI); IR, incidence rate per 1000 person-years; OA, osteoarthritis.

release of tryptase mediates synovitis and joint tissue breakdown in OA<sup>6,29,30</sup>; (3) genomic analyses have identified associations between IL-4 and IL-4 receptor gene polymorphisms and the development of OA.<sup>8–10,31</sup> Furthermore, increased mast cell numbers and elevated tryptase have also been implicated in asthma pathogenesis.<sup>32</sup> Taken together, we hypothesise that pathways involved in atopic disease may contribute to the development of OA.

In support of our results, prior work has shown an increased prevalence of OA in patients with asthma compared with patients with COPD and control patients.<sup>33</sup> This prior study was limited by a small sample size, which included 425 patients with asthma (135 with OA) and 1131 patients with COPD (201 with OA). The cross-sectional nature of this prior study limited its ability to draw conclusions about the order of disease accrual and therefore whether atopic disease directly contributed to the development of OA. The findings of this prior study are supportive of our results; however, we extend the analysis to include the use of two independent, much larger cohorts, which include patients with atopic dermatitis in addition to asthma. Furthermore, the design of our study allows us to identify patients in whom the diagnosis of atopic disease definitively comes before the diagnosis of OA.

The strengths of our study include a large sample size and validation of the results in an independent cohort. We were able to adjust for age, sex, Charlson Comorbidity Score, and outpatient visit frequency, which are all potential confounders of the relationship between atopic disease and OA. In the STARR cohort, we were able to further adjust for BMI, which confirmed the results in Optum CDM. Using COPD as a respiratory comparator disease to asthma, we demonstrated a strong association between asthma and the development of OA. Rheumatoid arthritis, which has a distinct pathophysiology from OA, has been shown to be associated with both asthma and COPD.<sup>34</sup> Our study demonstrated a strong association between asthma and OA, but not between COPD and OA, further supporting the hypothesis that type 2 immune responses specifically contribute to the risk of developing OA, not pulmonary disease in general.

Our study has several limitations. First, this is a retrospective study using claims data, and there may be residual or unmeasured confounders. In order to address this, we used propensity score matching to balance the covariates, and we adjusted for baseline characteristics, including age, sex, race/ethnicity, Charlson Comorbidity Score, outpatient visit frequency and the duration of follow-up. However, despite these efforts, the fact that the STARR cohort demonstrated that the risk of OA was attenuated after adjusting for BMI, given that asthma and atopic dermatitis are obesity related, supports the possibility of additional confounders.

Second, in the Optum CDM dataset, we did not have data on important variables such as BMI, history of trauma to the joints or level of physical activity. We conducted a second analysis using electronic health record data in which we were able to adjust for BMI, which yielded similar trends. In addition, in the Optum CDM cohort for which we lacked BMI data, we found an increased risk of developing hand OA in patients with atopic disease compared with controls, and this manifestation of OA is not strongly or consistently associated with BMI.

Third, our use of ICD codes might have resulted in misclassification of exposures and outcomes. We believe this is likely to be non-differential between the two groups. Patients with atopic disease had a higher mean Charlson Comorbidity Score and a higher number of yearly outpatient visits compared with non-exposed patients, which could have biased the results in either

direction. If patients with atopic disease accrued more ICD codes due to more frequent visits, they might have been more likely to collect a diagnosis code for OA, biasing the results in favour of the hypothesis that atopic disease contributes to OA. If patients with atopic disease were sicker and therefore had additional non-OA ICD codes used to justify visits, OA might not have been coded, biasing the results towards the null. Further, we used a case finding approach for OA that is highly specific but not sensitive, and therefore might have missed incident OA cases. We assume that those missed were not differentially those with allergic or non-allergic conditions.

Fourth, we did not have data regarding the severity of atopic disease, the severity of OA or any information about commonly used over-the-counter treatments for atopic disease (ie, antihistamines) or OA (ie, non-steroidal anti-inflammatory drugs (NSAIDs)). However, we were able to adjust for outpatient visit frequency and the Charlson Comorbidity Score, which may serve as proxies for disease severity. Despite this, if there is differential NSAID use in patients with atopic disease (ie, some consider NSAIDs contraindicated in asthma), OA severity might be higher in the atopic disease group and account for some of the differences seen.

Fifth, it is difficult to separate the effect of atopic disease from the potential medication used to treat atopic disease, and thus we cannot definitively conclude that the association we observe is due to atopic disease itself.

Sixth, we selected for patients with incident atopic disease to define a 2-year period before the first diagnosis of atopic disease in which we could rule out pre-existing OA. By excluding prevalent atopic disease at the time of enrolment in the dataset, we might have selected patients who developed atopic disease later in life, thus affecting generalisability. However, this provided confidence that the exposure of atopic disease came before the outcome of OA. In addition, we believe that excluding patients with longstanding atopic disease likely led to an underestimation of the association between atopic disease and the development of OA.

Lastly, our study assumes that a patient has developed incident OA at the time of receiving an ICD code for OA, which might not be the case. It is possible that our outcome more accurately assesses when a patient has developed symptomatic OA to a large enough degree that the clinician acknowledges it through ICD coding.

In conclusion, patients with atopic disease have an increased risk of developing OA compared with the general population. The association between atopic disease and OA is supported by recent observations that mast cells and type II cytokines may play important roles in the pathogenesis of OA broadly, not just in patients with atopic disease. Our findings provide further support for the concept that allergic pathways may contribute to the development of OA. If this is indeed true, non-atopic patients may also benefit from the use of treatments that inhibit mast cells and allergic cytokines to treat or prevent OA.

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