Asthma and Proinflammatory Conditions: A Population-Based Retrospective Matched Cohort Study

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Abstract

Objective: To determine the association between asthma and proinflammatory conditions.

Participants and Methods: This population-based retrospective matched cohort study enrolled all asthmatic patients among Rochester, Minnesota, residents between January 1, 1964, and December 31, 1983. For each asthmatic patient, 2 age-and sex-matched nonasthmatic individuals were drawn from the same population. The asthmatic and nonasthmatic cohorts were followed forward in the Rochester Epidemiology Project diagnostic index for inflammatory bowel disease (IBD), rheumatoid arthritis (RA), diabetes mellitus (DM), and coronary heart disease (CHD) as outcome events. Data were fitted to Cox proportional hazards models.

Results: We identified 2392 asthmatic patients and 4784 nonasthmatic controls. Of the asthmatic patients, 1356 (57%) were male, and mean age at asthma onset was 15.1 years. Incidence rates of IBD, RA, DM, and CHD in nonasthmatic controls were 32.8, 175.9, 132.0, and 389.7 per 100,000 person-years, respectively; those for asthmatic patients were 41.4, 227.9, 282.6, and 563.7 per 100,000 person-years, respectively. Asthma was associated with increased risks of DM (hazard ratio, 2.11; 95% confidence interval, 1.43-3.13; $P<.001$) and CHD (hazard ratio, 1.47; 95% confidence interval, 1.05-2.06; $P=.02$) but not with increased risks of IBD or RA.

Conclusion: Although asthma is a helper T cell type 2–predominant condition, it may increase the risks of helper T cell type 1–polarized proinflammatory conditions, such as CHD and DM. Physicians who care for asthmatic patients need to address these unrecognized risks in asthmatic patients.

A sthma is the most common chronic illness in childhood and a major cause of morbidity in adults, affecting 4% to 17% of children and 7.3% to 10.1% of adults in the United States[1,2] and, overall, nearly 30 million Americans and 300 million people globally.[3] Asthma prevalence continues to increase in many parts of the world.[4] For example, the Centers for Disease Control and Prevention reported that the asthma prevalence in persons of all ages in the United States increased from 7.3% in 2001 to 8.2% in 2009, a 12.3% increase in 8 years.[5] The total incremental cost of asthma to society was estimated to be $56 billion,[6] suggesting that asthma is a major medical and economic burden globally.

There have been numerous studies concerning the etiology of asthma, but the effect of asthma on the epidemiologic characteristics of other chronic diseases has been relatively underinvestigated. There have been studies that assessed the relationship between asthma and chronic conditions (ie, proinflammatory conditions), such as rheumatoid arthritis (RA),[7-9] inflammatory bowel disease (IBD),[9-12] diabetes mellitus (DM),[8,9,13-16] and coronary heart disease (CHD).[14] However, most of these studies were based on cross-sectional studies using *International Classification of Diseases (ICD)* codes for asthma and chronic diseases as outcomes. To our knowledge, no population-based cohort study has examined the effect of asthma using predetermined criteria on the incidence of these proinflammatory conditions. Considering the major burden and major effects of these proinflammatory conditions, the study results have important implications on clinical practice and public health.

We hypothesized that there may be an inverse relationship between asthma as a helper T cell (T_H) type 2–polarized condition and proinflammatory diseases as T_H1-predominant immune conditions given the reciprocal regulation between T_H1 and T_H2.[17,18] To test this hypothesis, we conducted a population-based retrospective matched cohort study in Rochester, Minnesota, that determined the association of asthma with RA, IBD, DM, and CHD.

PARTICIPANTS AND METHODS

This study was designed as a population-based retrospective matched cohort study and was approved

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by the institutional review boards at Mayo Clinic and Olmsted Medical Center. We compared the incidence rates of proinflammatory conditions between Rochester residents with asthma (exposed group) and those without asthma (unexposed group) between January 1, 1964, and December 31, 1983.

Study Population and Setting

Rochester is centrally located in Olmsted County. During the study period, characteristics of the City of Rochester and Olmsted County populations were similar to those of the US white population except that a higher proportion of the working population is employed in the health care industry.[19-21] Rochester is an excellent setting in which to conduct a population-based epidemiologic study because medical care is virtually self-contained within the

community. In addition, when patients register at any health care provider in the community for the first time (eg, as newborns), they are asked whether they authorize using their medical records for research. Each patient who grants authorization (95%) for the use of their medical records for research is assigned a unique identifier under the auspices of the Rochester Epidemiology Project (REP),[22] which has been continuously funded and maintained since 1960. All clinical diagnoses are electronically indexed, and information from every episode of care is contained in detailed patient-based medical records; essentially, all medical care settings and providers are linked. This unique longitudinal population-based resource has been the source of more than 2000 publications on the epidemiologic study of disease.[23] Using REP resources, we previously demonstrated that incidence rates of asthma for this community are similar to those for other communities. For example, the annual incidence rate of asthma in Rochester was 238 cases per 100,000 persons, which is comparable with that in other communities, such as Tecumseh, Michigan (250 cases per 100,000 persons), during the study period.[24]

Exposure Ascertainment (Asthma)

The methods used to determine asthma status were previously reported.[21,25] We enrolled a previously assembled cohort of all asthmatic patients as an exposed group (study cohort) among the Rochester residents between 1964 and 1983. Although the study period was not recent, it was a population-based asthma cohort based on ascertainment of asthma using predetermined criteria for asthma (not *ICD* codes or self-report). This unique asthma cohort also allowed us to examine more clearly the effect of asthma on the risk of proinflammatory conditions. This period was before the introduction and widespread use of anti-inflammatory therapeutics, which might alter the relationship between asthma and the risk of proinflammatory conditions. To assemble this asthmatic cohort, a previous study identified all individuals with a potential asthma diagnosis and symptoms such as wheezing using the REP medical diagnostic list. Then the medical records for all potential asthmatic patients were reviewed to confirm asthma using predetermined criteria (Table 1). Diagnostic categories have been linked across the many updates of the diagnostic indices, including revisions of the *ICD* or *Hospital International Classification of Diseases Adapted* and Berkson codes. Of the 18,000 potential patients with asthma, 2499 met the criteria for asthma delineated in Table 1. In this study, we used this previously assembled asthma cohort (1964-1983).

TABLE 1. Definition of Asthma[a,b]

1. History of cough, dyspnea, or wheezing OR history of cough or dyspnea plus wheezing on examination

2. Substantial variability in symptoms from time to time or periods of weeks or more when symptoms were absent

3. Two or more of the following:

   Sleep disturbance by nocturnal cough and wheeze

   Nonsmoker (age ≥14 y)

   Nasal polyps

   Blood eosinophil count >300/μL

   Positive wheal and flare skin test results OR elevated serum IgE level

   History of hay fever or infantile eczema OR cough, dyspnea, and wheezing regularly on exposure to an antigen

   Pulmonary function tests showing an FEV_1 or FVC <70% of predicted and another with ≥20% improvement to an FEV_1 >70% of predicted OR a methacholine challenge test showing a ≥20% decrease in FEV_1

   Favorable clinical response to bronchodilator therapy

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

   Pulmonary function tests that showed FEV_1 to be consistently <50% of predicted or diminished diffusion capacity

   Tracheobronchial foreign body on or about the incidence date

   Hypogammaglobulinemia (IgG level <2.0 mg/mL) or another immunodeficiency disorder

   Wheezing occurring only in response to anesthesia or medication administration

   Bullous emphysema or pulmonary fibrosis on chest radiography

   PiZZ α_1-antitrypsin

   Cystic fibrosis

   Other major chest disease, such as juvenile kyphoscoliosis or bronchiectasis

[a] FEV_1 = forced expiratory volume in 1 second; FVC = forced vital capacity.
[b] Patients were considered to have definite asthma if a physician had made a diagnosis of asthma or if each of the 3 conditions were present, and they were considered to have probable asthma if only the first 2 conditions were present.

Excluded from the original study were (1) non-Rochester residents (to exclude referral patients from elsewhere), (2) those without research authorization for using medical records for research, and (3) individuals with any of the medical conditions listed in Table 1, which make ascertainment of asthma difficult.

Selection of Nonasthmatic Controls (Unexposed Group)

The REP resources were also used to generate a list of all Rochester residents without asthma (unexposed group) by excluding those who met the criteria for asthma (exposed group). Two nonasthmatic individuals as an unexposed group were matched to each corresponding asthmatic patient as an exposed group regarding sex and birthday (within 2 months for <18 years of age and within 1 year for ≥18 years of age) as the date criteria for asthma were first met by the case (ie, the patient's index date). Other criteria for nonasthmatic controls (unexposed group) included having been registered at Mayo Clinic as a resident of Rochester in the index year (±1 year) of their matched case. The index date for nonasthmatic controls was the closest clinic visit or hospitalization day to the index date of asthma for their matched case. Therefore, we ensured that asthmatic patients and nonasthmatic controls had a similar starting point of follow-up. The exclusion criteria for the unexposed group were the same as those for the exposed group.

Identification of Proinflammatory Conditions (Outcomes or Diseases)

Asthmatic patients (exposed group) and nonasthmatic controls (unexposed group or comparison cohort) who refused authorization for the use of medical records in research (typically 5%-6% in REP studies) were excluded from the study. We followed the exposed and nonexposed cohorts from the index date until the earliest of emigration, death, or the end of the study (December 31, 1983) to compare the cumulative incidence of the outcome disease of interest. We included only incident cases of proinflammatory conditions based on diagnostic codes by excluding the prevalent cases of proinflammatory conditions before the index date of asthma.

Ascertainment of IBD, DM, CHD, and RA as outcome events was based on the REP diagnostic index codes (*ICD* and Berkson codes) for individuals with IBD,[26-30] DM,[31-34] CHD,[35-37] and RA[38-40] from the medical record. Briefly, all medical index codes for DM that included a diagnosis of DM and DM-related complications (eg, diabetic retinopathy, nephropathy, gastroparesis, neuropathy, and ketoacidosis) were used. Similarly, all diagnostic index codes pertaining to angina pectoris, coronary disease, coronary atherosclerosis, myocardial infarction, and ischemic heart diseases were included for identification of CHD. All medical index codes for IBD including a diagnosis of IBD (eg, Crohn disease, ulcerative colitis, regional enteritis, regional jejunitis or ileitis, and IBD) were used. The REP computerized diagnostic index was searched for any diagnosis of RA (excluding degenerative arthritis or osteoarthritis and juvenile RA).

Statistical Analyses

The incidence rates and their corresponding 95% confidence intervals (CIs) of CHD, DM, RA, and IBD were calculated using the number of outcome events as the numerator and the total number of person-years of follow-up as the denominator. Since RA did not include juvenile RA and CHD is rare in children, we calculated the incidence rates of RA and CHD based on adult participants only. The incidence rate of each condition was compared between individuals with and those without asthma using nonasthmatic individuals as a reference group. We applied survival analysis using the Kaplan-Meier curve to compare survival free of outcome events between the asthmatic and nonasthmatic groups. Cox proportional hazards models were fit to calculate the hazard ratios (HRs) and their corresponding 95% CIs, adjusting for race/ethnicity. All the tests were 2-sided, with significance set at $P<.05$, and were performed using a commercially available software program (SAS, version 9.1; SAS Institute, Inc, Cary, NC).

RESULTS

Study Participants

Of the original asthma study cohort (n=2499), 107 patients were excluded (72 owing to no research authorization for the present study and 35 owing to mismatching of clinic number). Demographic characteristics are summarized in Table 2. In this study, 2392 patients with asthma and 4784 controls without asthma were enrolled. Of the asthmatic patients, 1356 (57%) were male, and 1074 of 1099 patients with known race/ethnicity (98%) were white. The median and mean ages at asthma onset were 5 and 15.1 years, respectively. The median (and interquartile range) follow-up durations after the index date of asthma in asthmatic patients and nonasthmatic controls were 7.0 years (2.9-13.2 years) and 5.8 years (1.9-12.0 years), respectively ($P=.001$).

Asthma and Proinflammatory Conditions

The incidence rates of IBD, RA, DM, and CHD in the nonexposed group were 32.8, 175.9, 132.0, and

TABLE 2. Demographic and Clinical Characteristics of the Study Participants[a]

	Asthmatic group (N=2392)	Nonasthmatic group (N=4784)
Age at index date (y)[b]		
Mean ± SD	15.1±20.5	15.1±20.5
Median (IQR)	5 (1-22)	5 (1-22)
Age group at last follow-up or at the end of the study, No. (%)		
Children (<18 y)	1082 (45)	2094 (44)
Adults (≥18 y)	1310 (55)	2690 (56)
Male sex, No. (%)	1356 (57)	2712 (57)
White race, No. (%)[c]	1074 (98)	1771 (91)

[a] IQR = interquartile range.
[b] The closest clinic visit date of nonasthmatic controls (unexposed group) was matched to the index date of their corresponding asthmatic patients (exposed group).
[c] The proportion of race/ethnicity was based on known race/ethnicity data for asthmatic patients (n=1099, 46%) and nonasthmatic controls (n=1948, 41%).

389.7 per 100,000 person-years, respectively, and those for the exposed group were 41.4, 227.9, 282.6, and 563.7 per 100,000 person-years, respectively. The main results are summarized in Tables 3 and 4 and in Figures 1 to 3. (Although median follow-up was 7.0 years for asthmatic patients and 5.8 years for nonasthmatic individuals, the data presented in Figures 1 to 3 show cumulative incidence rates throughout the study period of 20 years.) Asthma status was associated with increased risks of DM (unadjusted HR, 2.11; 95% CI, 1.43-3.13; $P<.001$) and CHD (unadjusted HR, 1.47; 95% CI, 1.05-2.06; $P=.02$), whereas individuals with asthma did not have significantly increased risks of IBD (unadjusted HR, 1.31; 95% CI, 0.53-3.25; $P=.56$) and RA (unadjusted HR, 1.30; 95% CI, 0.78-2.18; $P=.31$). Based on participants whose race/ethnicity was known, white race was associated with asthma ($P<.001$) (Table 2). However, after ad-

justing for race/ethnicity, there were no significant changes in the HRs for the association of asthma status with the risks of CHD and DM in multivariate Cox models (Table 4), and white patients had a lower risk of CHD compared with nonwhite patients (HR, 0.26; 95% CI, 0.17-0.40). The survival curves show that the incidence of CHD and DM in asthmatic patients continued to increase with increasing years of follow-up. Although there were trends toward a higher incidence of IBD and RA in asthmatic patients compared with nonasthmatic controls during the later follow-up period, there were no significant associations between asthma and the risk of RA or IBD.

DISCUSSION

Contrary to the original hypothesis that asthma, a T_H2-predominant condition, may have inverse relationships with proinflammatory conditions with T_H1 immune milieu, these study results showed increased risks of certain proinflammatory conditions, such as CHD and DM. We observed significant associations between asthma as the explanatory variable and the risk of CHD (adjusted HR, 1.46) and DM (adjusted HR, 2.12) even after controlling for race/ethnicity. However, we did not observe similar associations between asthma and risks of RA and IBD, although there were trends toward a positive association. The associations between asthma and these conditions might be due to detection bias since comorbid conditions in asthmatic patients might be more likely to be detected by physicians than those in nonasthmatic individuals, who may not require medical care as often. However, we do not believe that detection bias entirely accounts for the findings because ascertainment of asthma in this study was not based on a physician diagnosis or self-report but rather on predetermined criteria for asthma. In addition, detection bias is more likely to occur when outcome diseases are subclinical and

TABLE 3. Incidence Rates and 95% CIs of Outcome Events in Individuals With and Without Asthma[a,b]

	Children[c]		Adults[c]	
Outcome	With asthma	Without asthma	With asthma	Without asthma
CHD	NA	NA	563.7 (431.2-724.1)	389.7 (307.5-487.1)
DM	60.0 (19.5-139.8)	48.4 (19.5-99.6)	454.7 (336.3-601.2)	193.6 (137-265.7)
RA	NA	NA	227.9 (147.4-336.4)	175.9 (122.5-244.7)
IBD	12.0 (0.3-66.6)	13.8 (1.7-49.8)	63.7 (25.6-131)	45.1 (20.6-85.7)

[a] CHD = coronary heart disease; CI = confidence interval; DM = diabetes mellitus; IBD = inflammatory bowel disease; NA, not applicable; RA = rheumatoid arthritis.
[b] The incidence rates and their corresponding 95% CIs were calculated per 100,000 person-years.
[c] Stratification of age group was based on age at last follow-up or at the end of the study.

TABLE 4. Multivariate Cox Models for the Association Between Asthma and Proinflammatory Conditions [a,b]

Outcome	Unadjusted HR (95% CI)	P value	Adjusted HR (95% CI)[c]	P value
DM	2.11 (1.43-3.13)	<.001	2.12 (1.43-3.14)	<.001
CHD	1.47 (1.05-2.06)	.02	1.50 (1.07-2.10)	.02
RA	1.30 (0.78-2.18)	.31	1.30 (0.78-2.18)	.31
IBD	1.31 (0.53-3.25)	.56	1.30 (0.52-3.23)	.58

[a] CHD = coronary heart disease; CI = confidence interval; DM = diabetes mellitus; HR = hazard ratio; IBD = inflammatory bowel disease; RA = rheumatoid arthritis.

[b] The HRs and 95% CIs for the association between white race and risks of DM, CHD, RA, and IBD in the Cox models for adjustment were 0.85 (0.57-1.26), 0.26 (0.17-0.40), 0.93 (0.59-1.46), and 1.69 (0.68-4.22), respectively.

[c] Adjusted HRs for the association between asthma and risks of proinflammatory conditions controlling for race/ethnicity (white vs nonwhite).

their detections depend on screening tests or evaluations by physicians prompted by exposure status. However, the outcome events in this study, such as DM and CHD, are unlikely to go undetected for a period of time. In addition, our previous work showed that the role of detection bias in epidemiologic research concerning the association of asthma with other disease outcomes is minimal or unlikely. For example, we showed similar health care use between asthmatic patients and nonasthmatic controls, suggesting that asthma status does not influence health care use or affect the likelihood of detecting health outcomes differentially between asthmatic patients and nonasthmatic controls in this study setting.[41-44]

In support of these study findings, previous studies have demonstrated an association between asthma and CHD[14] and DM.[8,14-16] Thus, the present study results provide an important basis for the

potential association between asthma and proinflammatory conditions, although the present study results were not fully adjusted for all pertinent covariates or confounders.

When comparing the incidence rates of CHD and DM reported in previous studies conducted in the Rochester community (571-699 per 100,000 person-year[36] and 240-256 per 100,000 person-years,[33] respectively), the incidence rates of CHD and DM in the present study (390-564 per 100,000 person-years and 132-283 per 100,000 person-years, respectively) seem to be similar or slightly lower. The previous studies included older participants (ie, >30-35 years of age) than the present study, and the mean age of individuals in these previous studies were likely to be older than the present study patients. On the other hand, the incidence rates of RA and IBD in this study (176-228 per 100,000 person-years and 12-64 per 100,000 per-
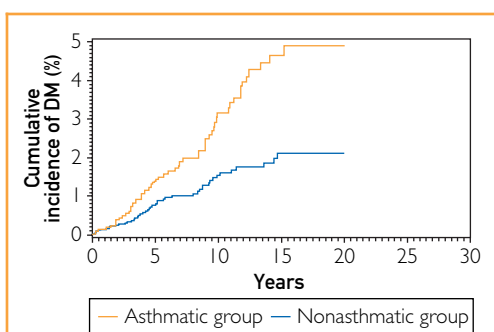

FIGURE 1. Cumulative incidence of diabetes mellitus (DM) in the asthmatic and nonasthmatic groups (P<.001 based on univariate Cox regression). The median (95% confidence interval) follow-up durations for the asthmatic and nonasthmatic groups were 7 (2.9-13.2) and 5.7 (1.9-12.0) years, respectively.
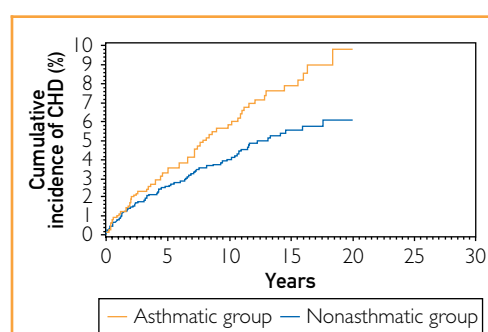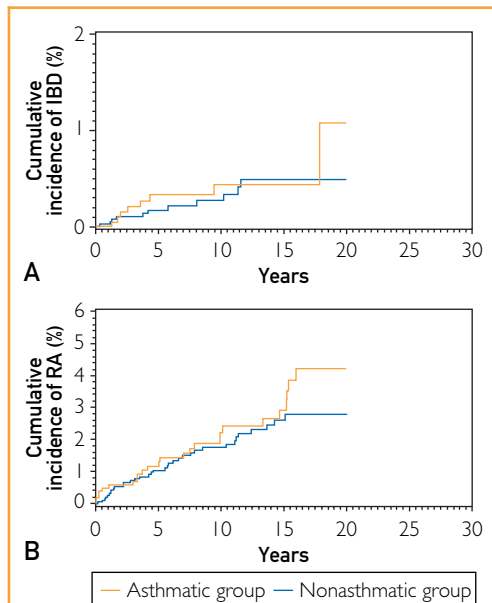

FIGURE 2. Cumulative incidence of coronary heart disease (CHD) in the asthmatic and nonasthmatic groups (P=.04 based on univariate Cox regression). The median (95% confidence interval) follow-up durations for the asthmatic and nonasthmatic groups were 7 (2.9-13.2) and 5.7 (1.9-12.0) years, respectively.

FIGURE 3. Cumulative incidence of inflammatory bowel disease (IBD) (A) and rheumatoid arthritis (RA) (B) in the asthmatic and nonasthmatic groups (no statistically significant differences). The median (95% confidence interval) follow-up durations for the asthmatic and nonasthmatic groups were 7 (2.9-13.2) and 5.7 (1.9-12.0) years, respectively.

son-years, respectively) were slightly higher than the incidence estimates reported in previous studies (75.3 per 100,000 person-years for RA,[40] 9.4-10.1 per 100,000 person-years for ulcerative colitis, and 6.5-7.9 per 100,000 person-years for Crohn disease[29]). Because of a smaller number of patients with IBD, we calculated the overall incidence of IBD only, which makes it difficult to compare with the standardized incidence of ulcerative colitis and Crohn disease of previous studies. Alternatively, the present study was based on the Rochester residents (urban setting), which has been reported to have a higher incidence of ulcerative colitis than a rural setting, whereas the previous study was based on Olmsted County residents (urban and rural residents).[30] Also, ascertainment of RA and IBD in previous studies was based on predetermined criteria for RA and IBD, whereas in the present study it was based on medical index search codes, which may inflate the incidence rate. However, this is likely to be subject to a nondifferential misclassification and is unlikely to affect the interpretation of the main results on the association of asthma with the risks of CHD and DM.

The lack of association between asthma and RA and IBD could be explained by statistical or potential immunologic reasons. The incidence rates of RA and IBD were lower than those of CHD and DM in adults, which may limit statistical power to detect the reported effect size.[29,33,36,40] Immunologically, during the study period, inhaled corticosteroids were not widely available for the treatment of asthma, and systemic corticosteroids were used for the treatment of asthma exacerbations and for asthma control. Systemic corticosteroid treatment for asthma might mitigate or slow the progress of RA and IBD (ie, may mask clinical symptoms for RA and IBD) in a way that attenuates the association of asthma with RA and IBD since systemic corticosteroids were a treatment choice for both conditions.

For the potential mechanisms underlying the associations of asthma with CHD and DM, we postulate potential intrinsic and extrinsic pathways. As an intrinsic mechanism, inflammatory cytokines, such as interleukin 6 and 17, have been reported to be involved in the inflammatory process in asthma[45-47] and proinflammatory conditions, including CHD[46,48] and DM.[49] As an extrinsic mechanism, acute exacerbations of asthma may cause hypoxia and tachyarrhythmia, triggering CHD symptoms. Thus, asthmatic patients with a predisposition to CHD may be more likely to reveal symptoms of CHD, leading to evaluations and detection of CHD. Similarly, corticosteroid treatment for asthma might cause steroid-induced hyperglycemia and is more likely to reveal those with immunogenetic predisposition to DM.

Overall, these epidemiologic data suggest that the traditional T_H1 vs T_H2 paradigm may not be a simple reciprocal inhibitory relationship in the context of development of chronic inflammatory diseases. Rather, asthma may share common underlying immunogenetic or environmental mechanisms with proinflammatory conditions. This conceptual understanding may facilitate clinical and basic research in a way that leads to improved patient care (early identification and better management of chronic diseases in asthmatic patients) and guidance for efforts to identify mechanisms underlying the association between asthma and proinflammatory conditions.

This study has the inherent limitations of a retrospective study. Although we adjusted the main results for age, sex, and ethnicity, we did not adjust for other potential covariates and confounders, such as body mass index, smoking, and other risk factors for CHD and DM. A future study examining the association between asthma and individual chronic conditions needs to consider these covariates and confounders. The present study participants were predominantly of white race, which may limit gen-

eralizability of the study findings. However, at the cost of generalizability (ie, external validity), internal validity can be enhanced by minimizing the confounding effect of race/ethnicity on the study results. The strengths of this study include a population-based matched cohort design that examined the incidence of proinflammatory conditions between asthmatic patients and nonasthmatic controls. In addition, we used a well-established epidemiologic database (ie, the REP) for proinflammatory conditions and applied predetermined criteria to determine asthma status. Also, the study setting has epidemiologic advantages, with a self-contained health care environment and unified medical records for research for all the residents of Rochester.

CONCLUSION

Asthma does not reduce the risk of proinflammatory conditions but increases the risk of CHD and DM. Physicians need to be aware of these study findings and address symptoms of CHD and DM in asthmatic patients during asthma follow-up visits. Also, given the considerable proportion of people affected by asthma, public health communities may need to carefully monitor the potential impact of asthma epidemiologic features on the epidemiologic mechanisms of the chronic diseases assessed in this study. Further studies that assess the association between asthma and individual chronic inflammatory conditions are needed to confirm these study findings.

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