

Asthma as a risk factor for zoster in adults: A population-based case-control study

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Background: We recently reported an increased risk of herpes zoster (shingles or zoster) in children with asthma, but little is known about whether the same is true for adults with asthma.

Objective: We determined whether asthma is associated with an increased risk of zoster in adults.

Methods: This study was designed as a population-based case-control study. Zoster cases during the study period were identified among adults (aged ≥ 50 years) who resided in Olmsted County, Minnesota. We compared the frequency of asthma between zoster cases and birthday- and sex-matched control subjects (1:2 matching) without a history of zoster. Asthma status was ascertained based on predetermined criteria. A conditional logistic regression model was used to assess the association of asthma with risk of zoster. **Results:** A total of 371 zoster cases and their 742 matched control subjects were enrolled. Of the 371 cases, 246 (66%) were female, 348 (94%) were white, and the mean $\pm$ SD age was 66.8 ± 10.7 years. Twenty-three percent ($n = 87$) of zoster cases had a history of asthma compared with 15% ($n = 114$) of control subjects. Controlling for pertinent covariates and confounders, there was a significant association between a history of asthma and risk of zoster (adjusted odds ratio, 1.70; 95% CI, 1.20-2.42; $P = .003$). The population attributable risk percentage for asthma was about 10%.

Conclusions: Asthma is an unrecognized risk factor for zoster in adults. Consideration should be given to immunizing adults with asthma aged more than 50 years as a target group. (*J Allergy Clin Immunol* 2015;■■■:■■■-■■■.)

Key words: Asthma, herpes zoster, risk, adults, epidemiology

Herpes zoster (zoster or shingles) is estimated to occur in up to 30% of all adults by age 80 years, with nearly 1 million cases a year in the United States.^{1,2} The decade of life with the largest number of cases is 50 to 59 years, causing significant loss of work and productivity.¹ Yawn et al¹ reported an increasing trend of the incidence of zoster in Olmsted County, Minnesota, over time (3.2 to 4.1 per 1000 person-years between 1996 and 2001).³ A prior study completed in Olmsted County using comparable data sources and definitions reported an incidence rate of 1.3 cases per 1000 person-years between 1945 and 1959, suggesting an increase of greater than 3-fold over the 56 years studied.⁴ Although the reasons for this increase in zoster rates are unknown, the introduction of the childhood varicella vaccination (1995) is unlikely to account for the increasing trends of zoster in our study setting.

Despite the presumed immunosenescence with aging,^{1,5,6} it is still unclear why some persons have zoster and others do not. Almost all (99.2% to 99.6%) of the US population aged 40 years or greater have serologic evidence for previous varicella infection and therefore are at risk for zoster,^{5,7} but two thirds of persons will never have zoster.¹ Only 8% to 10% of patients with zoster have known significant immune suppression, potentially suggesting unrecognized risk factors.¹ In this respect little is known about the effect of conditions with immune dysfunction, such as asthma, on the risk of zoster.

Asthma represents one of the 5 most burdensome chronic diseases in the United States,⁸ affecting 7% to 17% of the US population.⁸⁻¹² It increases the risk of serious and common microbial infections,¹³⁻¹⁹ which might in part be accounted for by suboptimal innate and adaptive immune functions.²⁰⁻²⁴ Thus we recently examined the relationship between asthma and the risk of zoster and found a significantly increased risk of zoster among children with asthma (adjusted odds ratio [OR], 2.07; 95% CI, 1.24-3.52).²⁵

This population-based study expands our exploration further to assess whether asthma status is associated with the risk of zoster in adults. This study provides an important insight into the nature of the effect of asthma on the risk of infections because zoster is a unique non-airway-related latent viral activation in dorsal root ganglia, which is primarily controlled by cell-mediated immunity.^{13,14,16,17}

METHODS

Study setting

Olmsted County, Minnesota, provides unique advantages for population-based epidemiologic studies because medical care is virtually self-contained within the community. In addition, when patients register with any health care

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Abbreviations used

ICS: Inhaled corticosteroid
OR: Odds ratio
REP: Rochester Epidemiology Project

providers in the community, they or their parents/legal guardians are asked to grant or refuse authorization of use of their medical records for research. Authorization is granted by more than 95% of all subjects.²⁶ Medical records research using the geographically defined population of Olmsted County was possible through the Rochester Epidemiology Project (REP), which has been continuously funded by the National Institutes of Health and maintained since 1960.²⁷⁻³⁰ Within the REP,³¹ each patient seen at any health care facility within the county has all diagnostic codes collected with health care services and site of service. This study protocol was approved by the institutional review boards at both Mayo Clinic and Olmsted County Medical Center.

Study design

The study was designed as a population-based case-control study, which compared the frequency of asthma before the index date among incident cases of zoster with that among birth date (± 1 year)-, sex-, initial clinic or hospital registration date-, and index date (± 1 year)-matched corresponding control subjects (1:2 individual matching) without a history of zoster. The index (incident) date for cases was the date of the first zoster diagnosis, and that for control subjects was the closest clinic visit date (within 1 year) to the index date of corresponding cases.

Case ascertainment

All potential zoster cases (≥ 50 years of age) occurring between January 1, 2010, and October 31, 2011, were identified from medical records by using a case ascertainment algorithm used for our previous study.^{1,32} All potential zoster incident cases were identified from a broad search of diagnostic codes (International Classification of Diseases, Ninth Revision, codes 053.xx) for zoster and zoster complications. Medical records regarding each potential incident case were reviewed to verify that the case was indeed a new case of zoster based on the criteria for zoster. Confirmation required either (1) positive laboratory data supported with a Tzanck smear, viral culture, or a positive PCR test for zoster virus or the following (2) clinical criteria used in our previous study: (A) a statement of characteristic rash (vesicular rash on dermatome) in medical records, (B) signs or a statement of pain or itching at the rash site during the interview, and (C) a physician's diagnosis of zoster in the medical record. Exclusion criteria included (1) subjects without research authorization; (2) non-Olmsted County, Minnesota, residents; (3) another diagnosis explaining the rash, such as culture positive for herpes simplex; and (4) clinical conditions making ascertainment of asthma difficult, as listed in Table I.

Selection of control subjects

Two matched control subjects were randomly selected from the REP (ie, population-based sampling frame for Olmsted County, Minnesota, residents). The literature showed that 99.2% to 99.6% of the US population aged 40 or more years has serologic evidence for previous varicella infection, which was quite steady over time (1988-2004).^{5,7} We did not assess serologic evidence for a history of varicella infection in the past for control subjects.

Determination of exposure status (asthma status)

We applied predetermined criteria for asthma delineated in Table I, which have been extensively used in research for asthma epidemiology and have shown excellent construct validity and reliability (0.72-0.92).^{13,14,17,18,33,34}

Because most subjects with probable asthma (85%) had definite asthma over time, we combined both probable and definite asthma.³³

Other variables

We collected pertinent variables for this study: asthma medication and control status, comorbid conditions at the time of the index date, other atopic conditions before the index date, zoster vaccination before the index date, and proxy measures for health care access (influenza vaccination in a preceding year and pneumococcal polysaccharide vaccination). The comorbid conditions examined in this study are listed in Table II. Other atopic conditions were ascertained by a diagnosis of atopic dermatitis, allergic rhinitis, and food allergy documented in medical records before the index date of zoster. We collected data on corticosteroid therapies and asthma control status within 6 months of the index date of zoster. We defined poorly controlled asthma as any asthma symptoms documented in medical records, systemic corticosteroid therapy for asthma symptoms, unscheduled visits for asthma, visits to the emergency department for asthma, or hospitalization for asthma within 6 months before the index date.^{35,36}

Data analysis

Matched analysis through conditional logistic regression was used, with zoster case status as the target end point in the model and asthma status as the primary explanatory variable. In each model the matching variables (age, sex, and years since registration) were included as adjusting covariates to control for any residual confounding not prevented by the matching. Asthma was carried forward into a multivariable model along with other factors screened from univariable modeling by using an α level of 0.2.³⁷ Atopic dermatitis, allergic rhinitis, and food allergy, which share similar immunologic characteristics with asthma, were left out of this model to avoid collinearity, although each was included in separate multivariable models (removing asthma) to test the association with zoster. We calculated the population attributable risk percentage of asthma for zoster.³⁸ We examined a differential effect of asthma on the risk of zoster among different age groups by assessing the statistical significance of the interaction term between asthma and age groups. Incidence of zoster was estimated among adults in the county during the 2-year study time frame, with rates adjusted for age and sex by means of direct standardization against the 2010 US population. All analyses were performed with SAS software (version 9.3; SAS Institute, Cary, NC).

RESULTS**Study subjects**

Of the total 475 potential zoster cases identified during the study period, 93 subjects were excluded from incidence analyses for the following reasons: non-Olmsted County residents ($n = 62$), no research authorization ($n = 19$), and no physician's diagnosis of zoster in medical records during the study period ($n = 12$). For analyses pertaining to the relationship between asthma and zoster, an additional 10 subjects were excluded because of clinical conditions making asthma ascertainment difficult (2 for pulmonary fibrosis, 2 for bronchiectasis, 5 for significantly decreased pulmonary function defined by an $FEV_1 < 50\%$ or diminished diffusion capacity, and 1 for significant scoliosis) and 1 because of insufficient medical records to determine asthma status.

Based on a total of 382 incident cases, the overall age- and sex-adjusted incidence rate of zoster during our study period was 4.3 (95% CI, 3.9-4.7) per 1000 person-years. The age-adjusted sex-specific incidence rates (per 1000 person-years) were 5.3 (95% CI, 4.7-6.0) in female subjects and 3.2 (95% CI, 2.7-3.8) in male subjects. The sex-adjusted age-specific incidence rates were 3.1 (95% CI, 2.6-3.7) in subjects aged 50 to 59 years, 4.5 (95% CI,

TABLE I. Definition of asthma

Patients were considered to have *definite* asthma if a physician made a diagnosis of asthma and/or if each of the following 2 conditions were present, and they were considered to have *probable* asthma if only the first 2 conditions were present:

1. history of cough with wheezing and/or dyspnea OR history of cough and/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; and
3. 2 or more of the following:
 - sleep disturbance caused by nocturnal cough and wheeze,
 - nonsmoker,
 - nasal polyps,
 - blood eosinophilia $>300/\mu\text{L}$,
 - positive wheal-and-flare skin test result OR increased serum IgE level,
 - history of hay fever or infantile eczema OR cough, dyspnea, and wheezing regularly on exposure to antigen,
 - pulmonary function tests showing 1 FEV₁ or FVC value of $<70\%$ of predicted value and another with $\geq 20\%$ improvement to an FEV₁ of $>70\%$ of predicted value OR a methacholine challenge test showing $\geq 20\%$ decrease in FEV₁, and
 - favorable clinical response to bronchodilator.

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

- pulmonary function tests that showed FEV₁ to be consistently $<50\%$ of predicted value or diminished diffusion capacity;
- tracheobronchial foreign body at or about the incidence date;
- hypogammaglobulinemia (IgG <2.0 mg/mL) or other immunodeficiency disorder;
- wheezing occurring only in response to anesthesia or medications;
- bullous emphysema or pulmonary fibrosis on chest radiograph;
- PiZZ α_1 -antitrypsin;
- cystic fibrosis;
- other major chest disease, such as juvenile kyphoscoliosis or bronchiectasis.

FVC, Forced vital capacity.

3.7-5.4) in those aged 60 to 69 years, and 5.8 (95% CI, 4.9-6.8) in those aged 70 years or older. The characteristics of the patients with zoster and their matched control subjects are summarized in [Table II](#).

Association between asthma and risk of zoster

We found a significant association between asthma and risk of zoster in our study population. The results are summarized in [Table III](#). Of the 371 zoster cases, 87 (23%) were in asthmatic patients compared with 114 (15%) of 744 control subjects who had asthma (OR, 1.73; 95% CI, 1.26-2.39; $P < .001$). The mean $\pm$ SD age at asthma onset was 49.1 ± 17.5 years (50.4 ± 16.8 years in zoster cases and 48.2 ± 18.0 years in control subjects). Adjusted for potential confounders identified from univariate models ([Table III](#)), the association between asthma and zoster remained significant (adjusted OR, 1.70; 95% CI, 1.20-2.42; $P = .003$; population attributable risk, 9.7%). Based on a test of interaction between asthma and age categories of less than 60 years ($n = 356$), 60 to 69 years ($n = 332$), and 70 or more years ($n = 425$), there was no evidence of a differential asthma effect across age strata ($P = .978$).

Associations of asthma control and inhaled corticosteroid use with risk of zoster

Inhaled corticosteroid (ICS) use was not shown to be a risk factor for zoster in our study population. Among all asthmatic patients in both the case and control groups ($n = 201$), only 11 (6%) were considered to have poorly controlled asthma at the time of zoster assessment, and 62 (31%) had been treated with ICSs, systemic corticosteroids, or both (the dose of ICS was defined by the National Asthma Education and Practice Program guidelines): 49 were receiving low-dose ICS (79%), 7 were

receiving medium-dose ICS (11%), 2 were receiving high-dose ICS (3%), and 4 were receiving high-dose ICS and oral corticosteroid (6%) therapy. Twenty-five (29%) of 87 zoster cases were treated with ICSs compared with 37 (32%) of 114 control subjects (OR, 0.83; 95% CI, 0.45-1.54; $P = .547$). Both inactive asthma (OR, 1.90; 95% CI, 1.21-3.00) and active (current) asthma (OR, 1.61; 95% CI, 1.07-2.41) were associated with increased risk of zoster compared with no asthma ($P = .003$), but there was no difference in the risk of zoster between patients with inactive and those with active asthma ($P = .61$). For asthma control status, 6 (7%) of 75 zoster cases and 5 (4%) of 114 control subjects had poorly controlled asthma (OR, 1.53; 95% CI, 0.44-5.25; $P = .501$).

Association of other factors with risk of zoster

From univariable analyses, the association of zoster was statistically significant for atopic dermatitis (OR, 1.71; 95% CI, 1.12-2.61; $P = .013$). In separate models that controlled for the same adjusting covariates in [Table III](#), the odds of zoster were significantly higher in patients with atopic dermatitis (adjusted OR, 1.72; 95% CI, 1.09-2.71; $P = .020$) than in those without. With asthma and other atopic conditions (allergic rhinitis and food allergy) additionally entered into the model, both asthma (adjusted OR, 1.54; 95% CI, 1.06-2.25; $P = .024$) and atopic dermatitis (adjusted OR, 1.63; 95% CI, 1.03-2.59; $P = .038$) were independently associated with risk of zoster. We also examined a potential interaction between asthma and atopic dermatitis in relation to the effect of asthma on the risk of zoster by stratifying the effect of asthma on the risk of zoster by atopic dermatitis status. Although there was no significant interaction ($P = .287$), the effect of asthma on the risk of zoster appeared to be greater among patients with atopic dermatitis (OR, 2.73; 95% CI, 1.02-7.29) than those without atopic dermatitis (OR, 1.55; 95% CI, 1.07-2.26). However, the associations of

TABLE II. Sociodemographic and clinical characteristics of subjects and their associations with risks of herpes zoster

Variable	Zoster cases (n = 371)	Control subjects (n = 742)
Female sex	246 (66%)	492 (66%)
Age at index date (y)	66.8 ± 10.8	66.8 ± 10.7
Age of asthma onset (y)	50.4 ± 16.8	48.2 ± 18.0
Years since registration	39.3 ± 17.3	41.5 ± 16.8
Ethnicity		
White/non-Hispanic	348 (94%)	683 (92%)
Nonwhite	18 (5%)	51 (7%)
Unknown	5 (1%)	8 (1%)
Education		
Less than high school	20 (5%)	31 (4%)
High school graduate	113 (30%)	240 (32%)
College	120 (32%)	225 (30%)
Postgraduate	107 (29%)	212 (29%)
Unknown	11 (3%)	34 (5%)
Asthma	87 (23%)	114 (15%)
Allergic rhinitis	129 (35%)	216 (29%)
Atopic dermatitis	45 (12%)	58 (8%)
Food allergy status	9 (2%)	10 (1%)
Comorbid conditions*		
Alcohol addiction	5 (1%)	24 (3%)
Autoimmune disease†	35 (9%)	44 (6%)
COPD	17 (5%)	24 (3%)
Chronic renal insufficiency	26 (7%)	41 (6%)
Cirrhosis	5 (1%)	10 (1%)
Congestive heart failure	12 (3%)	18 (2%)
Coronary artery disease	63 (17%)	106 (14%)
Diabetes mellitus	58 (16%)	133 (18%)
History of stroke	10 (3%)	38 (5%)
Hematologic cancer	28 (8%)	4 (1%)
Transplant recipient	2 (1%)	1 (0%)
Skin disease‡	18 (5%)	27 (4%)
Psychologic conditions§	84 (23%)	196 (26%)
Any comorbidity	208 (56%)	409 (55%)
Physical trauma	14 (4%)	9 (1%)
Smoking status		
Never smoked	194 (52%)	379 (51%)
Active smoker	17 (5%)	63 (8%)
Passive smoker	2 (1%)	4 (1%)
Exsmoker	156 (42%)	272 (37%)
Unknown	2 (1%)	24 (3%)
Influenza vaccination	253 (68%)	425 (57%)
Pneumococcal vaccination	193 (52%)	357 (48%)
History of zoster vaccination	83 (22%)	196 (26%)

COPD, Chronic obstructive pulmonary disease.

*Comorbid conditions are not mutually exclusive because some subjects had multiple comorbid conditions, and thus the sum of percentages is greater than the percentage correspondence to "any comorbidity."

†Autoimmune diseases include systemic lupus erythematosus, rheumatoid arthritis, and inflammatory bowel disease.

‡Skin disease includes any skin conditions other than atopic dermatitis, such as psoriasis.

§Psychologic conditions include a physician's diagnosis of psychologic/psychiatric conditions such as mood disorders, anxiety disorders, conduct or behavioral disorder, and adult attention deficit disorder.

food allergy ($P = .145$) and allergic rhinitis ($P = .070$) with the risk of zoster only approached statistical significance in the multivariate analysis. Subjects with a history of trauma and hematologic malignancy had an increased risk of zoster compared with those without such conditions. As expected, neither influenza vaccine nor pneumococcal vaccine was associated

with the risk of zoster, whereas zoster vaccine was associated with a lower risk of zoster.

DISCUSSION

This population-based study in adults upholds our previous finding on asthma as an independent risk factor for zoster in asthmatic children. This might also be true for other atopic conditions, such as atopic dermatitis. The effect of asthma on risk of infection might go beyond the airways.

The overall age- and sex-adjusted incidence rate of zoster in our study (4.3 [95% CI, 3.9-4.7] per 1000 person-years) was similar to the US incidence rate (2.8-4.4 depending on study years).³⁹ Our study results corroborated previously reported factors associated with the risk of zoster, such as female sex, immunocompromised conditions, mechanical trauma, and zoster vaccination.^{25,40-42}

Our study results on the association between asthma and risk of zoster (adjusted OR, 1.70; 95% CI, 1.20-2.42; $P = .003$) are unlikely to be due to a detection bias because all cases were population-based incident zoster cases and no significant differences were found in influenza and pneumococcal vaccinations before the index date of zoster between cases and control subjects as a surrogate measure for access to health care. Regardless, the estimated effect of asthma was adjusted for these variables. No significant differences in access to health care services (eg, general medical examination or evaluation for acute illnesses) between subjects with and without a physician's diagnosis of asthma were found in our study setting.^{17,43} Susceptibility bias might be an important concern given the relatively older population of our study subjects and higher comorbid conditions. To address this concern, we adjusted significant comorbid conditions individually, which were associated with the risk of zoster, as shown in Table III. Controlling comorbid conditions did not significantly change the effect size (1.73-1.70). Our study results suggest that there is no evidence of a differential effect of asthma across age strata. Although both active and inactive asthma were associated with the increased risk of zoster, asthma medications and control status did not influence the association, and this is consistent with the literature.⁴⁴ Finally, other atopic condition, such as atopic dermatitis (adjusted OR, 1.72; 95% CI, 1.09-2.71; $P = .020$), was associated with the risk of zoster, whereas both allergic rhinitis (adjusted OR, 1.30; 95% CI, 0.98-1.74; $P = .070$) and food allergy (adjusted OR, 2.05; 95% CI, 0.78-5.38; $P = .145$) approached statistical significance. When adjusted for atopic dermatitis, asthma was still significantly associated with the risk of zoster, and there was no significant interaction between asthma and atopic dermatitis in relation to the effect of asthma on the risk of zoster. These results suggest the effect of asthma on the risk of zoster is independent of atopic dermatitis. These results potentially suggest biological coherence with our main study findings on the association between asthma and the risk of zoster.

The results of this work are consistent with our previous study results on the increased risk of zoster among children with asthma (adjusted OR, 2.09; 95% CI, 1.24-3.52; $P = .006$).²⁵ Recent studies conducted in Spain and England characterized adults with zoster without an *a priori* hypothesis and showed that asthma was one of the conditions associated with an increased risk of zoster.^{45,46} In addition, previous studies showed increased risks of herpes simplex ocular infections^{47,48} and eczema herpeticum⁴⁹ among patients with atopic conditions.

TABLE III. Association between asthma and risk of herpes zoster in univariable and multivariable analyses

Variable	Matched analysis result, OR (95% CI)	
	Univariable models*	Multivariable model
Ethnicity	<i>P</i> = .313	
White/non-Hispanic	1.0 (reference)	
Nonwhite	0.65 (0.36-1.15)	
Unknown	1.18 (0.38-3.63)	
Education	<i>P</i> = .599	
Less than high school	1.0 (reference)	
High school graduate	0.81 (0.44-1.48)	
College	0.88 (0.48-1.59)	
Postgraduate	0.78 (0.42-1.45)	
Unknown	0.51 (0.21-1.25)	
Asthma	1.73 (1.26-2.39), <i>P</i> < .001	1.70 (1.20-2.42), <i>P</i> = .003
Allergic rhinitis†	1.30 (1.00-1.70), <i>P</i> = .054	
Atopic dermatitis†	1.71 (1.12-2.61), <i>P</i> = .013	
Food allergy status†	1.77 (0.71-4.38), <i>P</i> = .219	
Comorbid conditions‡		
Alcohol addiction	0.42 (0.15-1.13), <i>P</i> = .086	0.40 (0.14-1.17), <i>P</i> = .094
Autoimmune disease§	1.65 (1.03-2.64), <i>P</i> = .037	1.41 (0.84-2.38), <i>P</i> = .190
COPD	1.48 (0.77-2.84), <i>P</i> = .236	
Chronic renal insufficiency	1.35 (0.78-2.34), <i>P</i> = .284	
Cirrhosis	1.17 (0.39-3.48), <i>P</i> = .775	
Congestive heart failure	1.31 (0.59-2.90), <i>P</i> = .511	
Coronary artery disease	1.24 (0.86-1.79), <i>P</i> = .246	
Diabetes mellitus	0.83 (0.59-1.16), <i>P</i> = .271	
History of stroke	0.50 (0.25-1.03), <i>P</i> = .059	0.60 (0.28-1.27), <i>P</i> = .181
Hematologic cancer	13.88 (4.86-39.62), <i>P</i> < .001	13.75 (4.66-40.55), <i>P</i> < .001
Transplant recipients	5.78 (0.45-73.52), <i>P</i> = .176	5.89 (0.12-292.36), <i>P</i> = .373
Skin disease	1.36 (0.73-2.55), <i>P</i> = .329	
Psychologic conditions¶	0.80 (0.59-1.08), <i>P</i> = .148	0.79 (0.57-1.10), <i>P</i> = .159
Any comorbidity	1.04 (0.79-1.35), <i>P</i> = .794	
Trauma	3.06 (1.27-7.36), <i>P</i> = .013	2.72 (1.07-6.92), <i>P</i> = .036
Smoking status	<i>P</i> = .025	
Never smoked	1.0 (reference)	1.0 (reference)
Active smoker	0.58 (0.33-1.02)	0.60 (0.32-1.12)
Passive smoker	1.09 (0.19-6.08)	1.15 (0.20-6.59)
Exsmoker	1.13 (0.86-1.48)	1.27 (0.95-1.69)
Unknown	0.17 (0.04-0.75)	0.20 (0.05-0.89)
Influenza vaccination	1.05 (0.93-1.19), <i>P</i> = .402	

(Continued)

TABLE III. (Continued)

Variable	Matched analysis result, OR (95% CI)	
	Univariable models*	Multivariable model
Pneumococcal vaccination	1.33 (0.95-1.85), <i>P</i> = .092	1.14 (0.78-1.66), <i>P</i> = .497
History of zoster vaccination	0.77 (0.55-1.07), <i>P</i> = .124	0.68 (0.47-0.97), <i>P</i> = .035

COPD, Chronic obstructive pulmonary disease.

*Each model includes the matching variables sex, age, and years since registration as adjusting covariates.

†Other atopic conditions (eg, atopic dermatitis) were not included in this model testing the association of asthma with risk of zoster because of biological collinearity.

‡Comorbid conditions are not mutually exclusive because some subjects had multiple comorbid conditions.

§Autoimmune disease includes systemic lupus erythematosus, rheumatoid arthritis, and inflammatory bowel disease.

||Skin disease includes any skin conditions other than atopic dermatitis, such as psoriasis.

¶Psychologic conditions include a physician's diagnosis of mood disorders, anxiety disorders, conduct or behavioral disorder, and adult attention deficit disorder.

The mechanisms underlying the association between asthma and the risk of zoster are unknown. Waning cell-mediated immunity has been suggested to increase the risk of zoster,^{1,5,6} and asthma might play a role in waning of adaptive immunity.^{19,50} Asthma as a T_H2-predominant condition that results in reciprocal suppression of T_H1 immunity (cell-mediated immunity) could explain in part the association observed in our study.^{51,52} Because viral gene products are needed to establish and maintain latency and host responses (T-cell immunity) determine latency versus reactivation,⁵³ it is important to determine how asthma as a host factor influences the interaction between viral gene expression (eg, *ORF61* for varicella zoster virus) and host immune response (eg, IFN- α , IFN- β , and IFN- γ).^{54,55} Impairment in innate immune functions in the skin and airways is well documented in patients with asthma or atopic dermatitis.^{15,18,19} Although there is limited information on adaptive immune functions in asthmatic patients, there is some evidence that patients with asthma or other atopic conditions might have impairment or incompetence in cell-mediated immunity.^{19,21,56}

Clinicians and patients need to be aware that a history of asthma and atopic dermatitis might be unrecognized risk factors for zoster in both adults and children, although the underlying mechanisms are unknown. Neither asthma-related medications, such as corticosteroids, nor asthma control status affected the risk of zoster, although statistical power might be limited to address these associations. Given the large proportion of adults affected by asthma and the availability of an effective vaccine preventing zoster, consideration for immunizing adults with asthma or atopic dermatitis 50 years or older as a target group for zoster vaccine should be given.

The main strength of the study is the population-based study design, which is based on incident zoster cases, minimizing misclassification, as reflected in the similar incidence rate of zoster at the national level. Another important strength is the epidemiologic advantage of our study setting, with a self-contained health care environment and availability of all medical records for study subjects under the REP. Also, we used predetermined criteria for asthma (instead of self-report or

International Classification of Diseases, Ninth Revision, codes), which were extensively used for previous epidemiologic investigations for the association between asthma and the risk of various microbial infections, relating our current results to our previous research work and ensuring consistency and coherence.

Our study has limitations. Even if our study setting is self-contained and case identification was based on incident cases, we might have missed some zoster cases, and therefore the incidence of zoster could be underestimated. However, the incidence estimate in our study was similar to that at the national level.

Second, the study subjects were predominantly a white population, which might limit the generalizability of our results to other ethnic groups or study settings. In addition to the comparable incidence rates of zoster in our study setting with those at the national level, our study results corroborated previously reported risk factors for zoster, suggesting the suitability of our study subjects and setting in addressing the study question.

Third, asthma control status (ie, poorly controlled asthma) was ascertained based on medical chart review, resulting in the possibility of missing some asthma symptoms and/or administration of asthma medications unless the subjects visited the clinic or emergency department or were hospitalized for asthma and the use of asthma medications was documented in the medical record.

Finally, our study subjects were a relatively older population (mostly born in the 1940s, when asthma incidence was low^{57,58}), and thus comorbid conditions might be a significant confounder, and the relationship between asthma and risk of zoster might vary across age strata. The association between asthma and risk of zoster was adjusted for significant comorbid conditions, and there was not a differential effect of asthma across different age strata. Apart from this concern and a potential misclassification of chronic obstructive pulmonary disease as asthma, we limited our analysis to subjects without a history of smoking. Asthma status was still significantly associated with the risk of zoster (adjusted OR, 1.61; 95% CI, 1.00-2.57; $P = .048$).

In conclusion, asthma might be an unrecognized risk factor for zoster in adults, and the effect of asthma on the risk of microbial infections or immune dysfunction might go beyond the airways. This could be true also for atopic dermatitis. Consideration should be given to immunizing adults 50 years or older with asthma or atopic dermatitis as a target group for zoster vaccine.

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Clinical implications: Asthma is an unrecognized risk factor for herpes zoster in adults. Consideration should be given to immunizing asthmatic adults over 50 years of age as a target group.

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