

molecular epitope patterns with tumor antigens⁹; therefore, increased anti-tumor IgE antibodies may potentiate allergic responses.⁹

We found that allergy and asthma are negatively associated with cancer diagnoses before 50 years of age. Whether this association is attributable to confounding covariates that are not captured or an immunologically conferred cancer protection is not elucidated. We acknowledge that association is not proof of causation (or, in this case, protection). Further investigation of the cellular mechanisms, including IgE anticancer T_H2 responses, may be helpful in clarifying the underlying mechanism or pathway and potential clinical significance of this negative association. Prospective studies need to be performed to prove a truly causal association.

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Seasonal trends in asthma exacerbations

Are they the same in asthma subgroups?

Asthma exacerbations have seasonal patterns that may differ by age group.^{1–3} The proposed underlying causes of these seasonal variations include viral upper respiratory tract infections, ambient air pollutants, and climate changes with an increase in aeroallergens.⁴ The recognition of seasonal patterns may help with identification and avoidance of asthma triggers.

There is emerging literature on phenotyping asthma to further understand its pathophysiology and appropriate management. Both smoking and obesity have been associated with corticosteroid insensitivity and severe asthma symptoms.^{5–8} Little is known, however, regarding seasonal variations in both of these asthma subgroups. The objective of this study was to evaluate whether the seasonal trends in asthma exacerbations persist in subgroups of smokers and morbidly obese individuals.

The number of asthma exacerbations for each month during a period of 3 years (2015–2017) was extracted from the electronic health record of an academic community health care system in Ohio. The search for asthma exacerbation included any of the *International Classification of Disease* (ICD) diagnoses: mild intermittent, mild persistent, moderate persistent, severe persistent, and unspecified asthma with acute exacerbation. Outpatient, emergency department, and hospital admission diagnoses were included. Institutional review board approval was obtained from MetroHealth Medical Center in Cleveland, Ohio. The number of asthma exacerbations was plotted over time to evaluate seasonal trends in 3 age groups (≤ 18 years, 19–64 years, and ≥ 65 years). Asthma exacerbations were also plotted over time in adults (> 18 years of age) and stratified by body mass index (BMI; calculated as weight in kilograms divided by the square of height in meters) (< 40 or ≥ 40) and current smoking status. The overall trend of asthma exacerbations over time was evaluated by linear regression. The

Edwards test was used to assess for seasonality ($\alpha = 0.05$). Prais-Winsten regression with autocorrelation adjustment was performed in the morbidly obese and smoker subgroups after logarithmic transformation of the outcome variable (number of asthma exacerbations) using Stata statistical software, version 12.0 (StataCorp).

A total of 19,603 cases of asthma exacerbations were analyzed during the 3-year period (2015–2017). The population was 61.5% female and 38.5% male. Ethnicity was 16.9% Hispanic and 83.0% non-Hispanic, further categorized into 39.6% white, 58.7% African American, and 1.7% other.

The number of asthma exacerbations per month was stratified by age as shown in Figure 1. There was a statistically significant positive association between the number of asthma exacerbations and time in months in all age subgroups ($P < 0.05$), indicating an upward trend over time. The test of seasonality was statistically significant in all age groups ($P < 0.001$ for ≤ 18 years of age, $P < 0.001$ for 19–64 years of age, and $P = 0.001$ for ≥ 65 years of age). The angles of maximum rate were -18° (late November) and -22° (late November) for the 18 years or younger group and 19 to 64 years of age groups, respectively. However, the angle of maximum rate was $+67^\circ$ (late February) in the 65 years or older group.

There were 7948 asthma exacerbations in adults with a BMI less than 40 and 2825 exacerbations in adults with a BMI of 40 or greater. Seasonality of asthma exacerbations appeared to persist in adults when stratified by BMI ($P < 0.001$ with BMI < 40 and ≥ 40), which was also evident graphically (Fig 1). The angles of maximum rate were -19.9° (late November) and -0.87° (middle December) for the BMI groups of less than 40 and 40 or greater, respectively.

There were 3139 and 9333 asthma exacerbations in adult smokers and adult nonsmokers, respectively. The angle of maximum rate was -12.67° (early December) in adult nonsmokers and -36.21° (middle November) in adult smokers. Although the



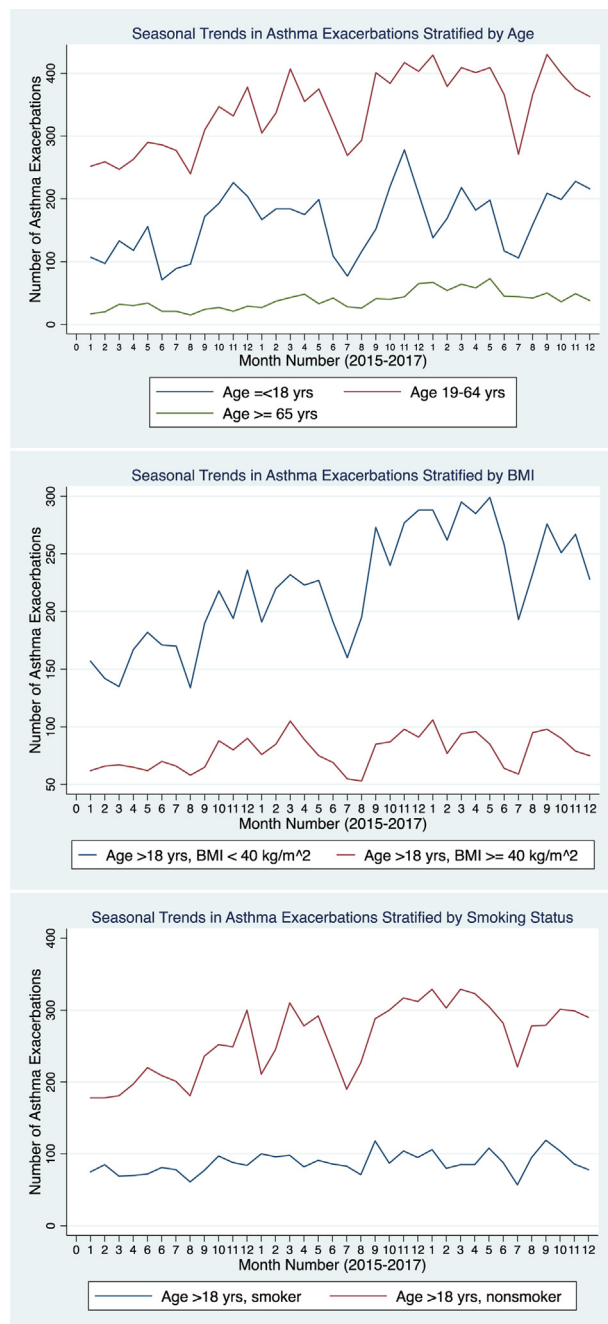


Figure 1. Time plot of asthma exacerbations stratified by age, BMI and smoking status.

seasonality test result was statistically significant in adult smokers ($P = 0.01$) and nonsmokers ($P < 0.001$), seasonal trends appeared less prominent in adult smokers by visual inspection of the time series graph (Fig 1).

Seasonal trends were further evaluated in the subgroups of interest (morbidly obese and smokers) with regression analysis that revealed a statistically significant negative association between the log of asthma exacerbations and month 7 (July) in the morbidly obese group ($P = 0.04$) but not in smokers ($P = 0.23$).

This study demonstrates seasonal variations of asthma exacerbations in all age groups, with a winter peak in elderly individuals and a fall peak in the other age groups. These findings are consistent with other studies that found different seasonal

asthma patterns with age group stratification.^{1–3} There are several limitations to this study. First, data are restricted to a single center in northeast Ohio. Second, the diagnoses of asthma exacerbations were based on ICD diagnoses, which may lead to misclassification bias. Third, asthma exacerbations were not stratified by the presence of allergic history, which plays an important role in the seasonal variations of asthma exacerbations. Fourth, the sample size did not allow for analysis of seasonality in the morbidly obese who smoke. Fifth, the interpretation of the overall upward trend of asthma exacerbations is limited by the study's dynamic population.

Seasonality of asthma exacerbations was statistically significant and appeared to be prominent in morbidly obese individuals ($\text{BMI} \geq 40$). There is mounting evidence that obesity represents a unique phenotype of asthma. Obesity is associated with severe asthma symptoms and increased medication use thought to be related to enhanced systemic inflammation and corticosteroid resistance.⁷ One study revealed that obese patients had improved asthma control after bariatric surgery and subsequent weight loss.⁸ Even though there is evidence that obese patients with asthma may behave differently than those with a normal BMI, in this study, seasonality of asthma flares appeared to persist in morbidly obese individuals ($\text{BMI} \geq 40$). Our results are consistent with a previous study by Schatz et al,⁹ which found an increased risk of asthma exacerbations in the fall and winter with increasing BMI.

Seasonal trends in asthma flares appear to be less prominent in adult smokers with asthma, with a less striking trough in July, which is highly noticeable in morbidly obese individuals. There is evidence that cigarette smoke increases permeability of the respiratory epithelium because of mucosal inflammation and damage.¹⁰ Exposure to the irritants of cigarette smoke with the associated mucosal inflammation year round may explain the less striking seasonal variation of asthma exacerbations in smokers.

Seasonal trends of asthma exacerbations appeared in all age groups in our population, with a late autumn peak in children and adults and a late winter peak in elderly individuals. Seasonality of exacerbations appeared to persist in the morbidly obese adults with asthma and may be less prominent in adult smokers with asthma. Further studies are needed to explore whether this finding is reproducible in other populations and to further investigate the etiology of these trends.

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Dupilumab improves asthma outcomes irrespective of frequency of previous asthma exacerbation history



Lack of control of moderate-to-severe asthma results in a substantial disease burden and poor quality of life for affected patients and represents a significant unmet clinical need.¹

Dupilumab is a fully human monoclonal antibody inhibiting the signaling of interleukin (IL)-4 and IL-13, key drivers of inflammation in type 2 inflammatory diseases such as asthma, allergic rhinitis, atopic dermatitis, and food allergies—conditions that frequently manifest as comorbidities²—and is approved in the United States for patients aged 12 years or older with moderate-to-severe eosinophilic or oral corticosteroid-dependent asthma^{3–5} and for the treatment of adults with inadequately controlled moderate-to-severe atopic dermatitis in several countries.^{6–8} In a pivotal, placebo-controlled, phase 2b study of uncontrolled persistent asthma in 769 adults without restrictions for absolute eosinophil count as an inclusion or exclusion criterion (NCT01854047), dupilumab administered subcutaneously at doses of 200 mg or 300 mg every 2 weeks or every 4 weeks with medium-to-high-dose inhaled corticosteroids plus a long-acting β_2 -agonist (ICS+LABA) improved lung function, as measured by the forced expiratory volume in 1 second (FEV₁), reduced annualized rates of severe asthma exacerbation, improved asthma control and measures of asthma-related quality of life, and was generally well tolerated.³

Asthma exacerbation history, particularly number of recent exacerbations, is considered a significant independent predictor of future exacerbation risk,⁹ and frequent exacerbations (defined as a deterioration of asthma requiring use of systemic corticosteroids for ≥ 3 days, or hospitalization or emergency room visit because of asthma, requiring systemic corticosteroids and confirmed by chart review) tend to be associated with poorer lung function, worse asthma control, and greater use of high-dose ICS+LABA.³ Other factors associated with frequent exacerbations include blood eosinophil count, bronchodilator responsiveness, body mass index, and comorbid chronic rhinosinusitis and gastroesophageal reflux disease.¹⁰

This post hoc analysis of the phase 2b asthma study (NCT01854047) assessed the effects of dupilumab (200 mg or 300 mg every 2 weeks), compared with placebo, on annualized rates of

severe asthma exacerbations, changes in lung function, asthma control, and quality of life in patients categorized by the number of exacerbations they had experienced in the year before study entry. In the study, 465 patients had had 1 or more exacerbations; 227, 2 or more; 122, 3 or more; and 62, 4 or more. The highest number of exacerbations in the year prior to the study was 20 in the overall study population, 20 in the placebo group, 15 in the dupilumab 300 mg group, and 12 in the dupilumab 200 mg group. The annualized rate of severe exacerbations during the 24-week treatment period was derived from a negative binomial model. Change from baseline in lung function, measured by FEV₁ at weeks 12 and 24, was analyzed using a mixed-effects model with a repeated-measures approach to determine least squares (LS) mean and standard error (SE), as previously described.⁷ Asthma control was assessed using the 5-item Asthma Control Questionnaire (ACQ-5), and patient-reported quality of life was assessed with the Asthma Quality of Life Questionnaire (AQLQ); again, a mixed-effects repeated-measures model was used to determine the LS mean ($\pm$ SE).⁴ Because this was an exploratory analysis, no attempt was made to control for type I errors. Safety was also evaluated across subgroups by using adverse event reports and laboratory assessments.

Treatment with either dose of dupilumab significantly reduced the annualized rate of severe exacerbations to a similar extent ($P < .05$ vs placebo), with greatest treatment effect observed in patients with the highest number of exacerbations in the previous year (Fig 1A). In patients receiving placebo, the number of exacerbations during the study increased with the number of historical exacerbations during the previous year (Fig 1A). Treatment with dupilumab 200 mg and 300 mg every 2 weeks dose regimens significantly improved FEV₁ at weeks 12 and 24 ($P < .05$ vs placebo) in all patients, except at week 12 in patients who received dupilumab 200 mg every 2 weeks and had experienced 4 or more exacerbations in the previous year ($P = .1227$; Fig 1B). In patients receiving dupilumab, the higher the number of prior exacerbations, the greater the improvement observed. In the placebo group, however, the higher the number of exacerbations in the previous year, the lesser were the improvements in FEV₁. At week 24, all patients receiving dupilumab experienced significantly improved asthma control ($P < .05$ vs placebo). The largest improvements in asthma control occurred in patients who had experienced the highest numbers of exacerbations in the previous year (eFig 1). Findings were similar for asthma-related quality of life; LS mean changes in AQLQ scores from baseline to week 24 showed improvement with both dupilumab regimens in all patients. Again, improvements increased with the number of prior exacerbations, particularly in patients receiving the higher dose of dupilumab (eFig 1). In the overall study population, dupilumab was well tolerated at either dose during the study; the incidence of treatment-emergent adverse events was similar across treatment groups and independent of exacerbation history.

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