

Overweight/Obesity and Risk of Seasonal Asthma Exacerbations

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What is already known about this topic? Patients who are obese are at increased risk of asthma exacerbations.

What does this article add to our knowledge? Obesity is particularly associated with an increased risk of fall and winter asthma exacerbations in adults but not in children.

How does this study impact current management guidelines? Adult patients who are obese should be carefully followed up for asthma exacerbations in the fall and winter, with consideration of evaluation for vitamin D deficiency and a possible change in controller therapy before these higher-risk seasons.

BACKGROUND: Obesity is associated with an increased risk for asthma exacerbations, but whether this risk is related to the season of exacerbation is not known.

OBJECTIVE: To determine the relationship of increased body mass index (BMI) to the season of asthma exacerbation.

METHODS: Study subjects were adult (aged 18–65 years) and children (aged 5–17 years) health plan members with persistent asthma in 2008 for whom a BMI measurement was available. BMI categories were normal (<25 kg/m²), overweight (25–29.9 kg/m²), and obese (≥ 30 kg/m²). Exacerbations were defined as oral corticosteroid dispensings linked to an asthma encounter in the spring, summer, fall, or winter of 2009.

RESULTS: The cohort included 17,316 adults and 10,700 children. There was a significant ($P < .05$) linear increase with BMI category in the proportion of adults with exacerbations in

every season and in the proportion of children with exacerbations during fall and winter. Relationships of overweight or obesity (vs normal weight) to fall and winter exacerbations remained significant in both adults and children after adjustment for sex and education. In a generalized estimating equation model, both BMI status and season (spring, fall, and winter) were related to exacerbations. Moreover, we noted a significant interaction in adults ($P = .03$) but not children ($P = .97$) of the BMI-exacerbation association by season (fall-winter vs spring-summer).

CONCLUSION: Higher BMI values increased the risk for asthma exacerbations in adults and children with persistent asthma, particularly for fall-winter exacerbations in adults. Potential mechanisms for these findings, including vitamin D status, viral infections, and corticosteroid responsiveness, merit further study. © 2013 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2013;1:618–22)

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Obesity is associated with increased asthma prevalence¹ and severity,^{2–4} and reduced asthma control.^{1,3,4} In their 1999 prospective cohort study that linked obesity to the risk of incident asthma, Camargo et al⁵ also noted that women who were obese and with asthma were significantly more likely to report a history of asthma hospitalization. Along these same lines, we recently demonstrated that adults who were obese³ and children⁴ are more likely to experience asthma exacerbations than their normal-weight counterparts.

The mechanism of the increased risk of asthma exacerbations in individuals who are obese is uncertain. One possibility would be vitamin D deficiency, which has been shown to be more common in individuals who are obese⁶ and which has been associated with increased viral infections⁷ and asthma exacerbations.^{8,9} Another possibility is decreased corticosteroid responsiveness, which has been demonstrated in several studies in individuals who were obese.^{10–12}

Because respiratory viral infections increase¹³ and vitamin D levels decrease¹⁴ in the fall and winter, a vitamin D related

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Conflicts of interest: R.S. Zeiger has stock options with DBV Technologies, is a member of the research advisory board of DBV Technologies, and has received consultancy fees from GlaxoSmithKline, Genentech, Novartis, National Heart Lung and Blood Institute/Penn State, Aerocrine, Sunovion, and Astra Zeneca; his institution has grants pending from Genentech, GlaxoSmithKline, Aerocrine, Merck, MedImmune, and Thermofisher. The rest of the authors declare that they have no relevant conflicts of interest.

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Abbreviations used

ANOVA- Analysis of variance

BMI- Body mass index

GEE- Generalized estimating equation

HEDIS- Healthcare Effectiveness Data and Information Set

ICD-9- International Classification of Diseases, Ninth Revision

KPSC- Kaiser Permanente Southern California

OR- Odds ratio

SD- Standard deviation

mechanism would predict a particular increase in fall-winter exacerbations in individuals who are obese. In contrast, a corticosteroid resistance related mechanism would not be expected to vary as much by season. No prior study has evaluated whether obesity increases the risk of exacerbations to the same degree in all seasons. Because it may have mechanistic and therapeutic implications, the purpose of this study was to determine the relationship of increased body mass index (BMI) to season of exacerbation in both children and adults with persistent asthma.

METHODS

Study design

This was a retrospective longitudinal database study. Information on patient demographics, health care utilization, and pharmacy dispenses were captured in the Kaiser Permanente Southern California (KPSC) Research Data Warehouse.

Patients

Study subjects were members of KPSC Health Plan aged 5-56 years who were continuously enrolled in 2008 and 2009 (either as new or as continuing members), had persistent asthma (see below for definition) in 2008, and for whom a BMI measurement was available. BMI categories were normal ($<25 \text{ kg/m}^2$), overweight ($25\text{-}29.9 \text{ kg/m}^2$), and obese ($\geq 30 \text{ kg/m}^2$) for adults and normal (<85 th percentile), overweight (85th to 94.9th percentile), and obese (≥ 95 th percentile) for children aged 5-17 years. KPSC is a large integrated health maintenance organization that serves approximately 3.5 million members in the southern California region. KPSC members comprise approximately 15% of the region's population. The study was approved by the KPSC Institutional Review Board.

Administrative data

From the Research Data Warehouse, the following information was captured for April 1, 2008, to March 31, 2009 (referred to as 2008 in the rest of the article), and April 1, 2009, to March 31, 2010 (referred to as 2009): (1) age, (2) sex, (3) hospitalization with asthma coded as a principal diagnosis (International Classification of Disease, Ninth Revision [ICD] 9 493.xx), (4) emergency department visit with asthma coded (ICD-9 493.xx) as a principal diagnosis, (5) outpatient visit with asthma coded (ICD-9 493.xx) as a diagnosis, (6) any oral corticosteroid dispensing, (7) any inhaled corticosteroid dispensing, and (8) address. We successfully linked more than 95% of the addresses of our enrollees to census block groups and assigned block group level education estimates in 2006 to patients by using the proprietary demographic estimates supplied by Nielsen Claritas, Inc. (<http://www.nielsen.com/us>).

Persistent asthma was defined based on the Healthcare Effectiveness Data and Information Set (HEDIS) criteria in

TABLE I. Characteristics of study population, stratified by BMI status: adults aged 18 y and older (n = 17,316)

Characteristic	BMI status			P value†
	Normal	Overweight	Obese	
No. (%)	3526 (20.4)	5179 (29.9)	8611 (49.7)	
Mean (SD) age (y)	38.1 ± 12.2	42.0 (10.4)	43.0 (9.7)	<.0001
% Female	68.8	54.0	65.3	<.0001
% >High school education*	65.6	57.3	48.4	<.0001
% Inhaled corticosteroids 2009	66.5	69.6	67.5	<.01

*Census block group level.

†ANOVA for continuous variables and χ^2 test for discrete variables.

2008, which is any of the following during the 12-month period¹⁵: (1) 4 or more asthma medication dispensings, (2) 1 or more emergency department visits or hospitalizations with a principal diagnosis of asthma, or (3) 4 or more asthma outpatient visits with 2 or more asthma medication dispensings. Patients with an encounter code for chronic obstructive pulmonary disease, emphysema, or chronic bronchitis during 2008 or 2009 were excluded per HEDIS criteria. Exacerbations were defined as oral corticosteroid dispensings within 7 days of an encounter coded with a diagnosis of an asthma exacerbation or uncontrolled asthma. Spring was defined as April to June, summer as July to September, fall as October to December, and winter as January to March.

Data analysis

Demographic information and inhaled corticosteroid dispensings were compared among patients in the 3 BMI categories (normal, overweight, and obese) by 1-way ANOVA (continuous variables) or χ^2 analyses (categorical variables). These comparisons were stratified by age group (adults aged ≥ 18 years vs children aged <18 years). Relationships of the season of exacerbation (vs no exacerbation during that season) to BMI category were evaluated by the χ^2 test for linear trend analysis. Two types of models were used for adjusted analyses. The first was a series of log-binomial models in adults and children separately, with exacerbations in each season as the outcomes and BMI category (overweight or obese vs normal weight), sex, education, and age (in adults) as predictors to examine the relationship of obese or overweight status to asthma exacerbation for each season. The second was a generalized estimating equation (GEE) model,¹⁶ also in adults and children separately. These GEE models were applied to examine the association between BMI categories (overweight or obese vs normal weight) and asthma exacerbations in 4 seasons (or spring-summer vs fall-winter) simultaneously. Interaction between BMI categories and seasonal exacerbations was assessed by including the product term into the model. Nominal 2-tailed statistical significance for all analyses was set at $P < .05$. All analyses were conducted by using SAS version 9.2 for Windows software (SAS Institute Inc, Cary, NC).

RESULTS

Sample characteristics

The cohort included 17,316 adult patients (80% overweight or obese) and 10,700 children (46% overweight or obese) (Tables I and II). Adult patients with asthma were more likely to be women, whereas children were more likely to be boys. Adult

TABLE II. Characteristics of study population, stratified by BMI status: children aged 5-17 y old (n = 10,700)

Characteristic	BMI status			P value†
	Normal	Overweight	Obese	
No. (%)	5790 (4.1)	1908 (17.8)	3,002 (28.1)	
Mean (SD) age (y)	10.0 (3.6)	10.1 (3.3)	10.1 (3.4)	.11
% Female	59.9	59.7	66.5	<.0001
% >High school education*	48.6	43.9	34.3	<.0001
% Inhaled corticosteroids 2009	63.4	63.4	64.1	.80

*Census block group level.

†ANOVA for continuous variables and χ^2 test for discrete variables.**TABLE III.** Relationship of BMI status in 2008 to exacerbations in 2009: adults aged 18 y and older

BMI	% 2009 Exacerbations				
	Any	Fall	Winter	Spring	Summer
Normal (n = 3526)	17.2	6.2	5.7	5.1	4.6
Overweight (n = 5179)	19.2	7.6	7.4	5.0	4.3
Obese (n = 8611)	22.1	8.3	8.4	6.3	5.8
P value*	<.0001	<.001	<.0001	<.01	<.001

* χ^2 test.

patients who were overweight or obese were significantly older than normal-weight patients (Table I). Adults who were overweight were significantly less likely to be women (Table I), but children who were obese were more likely to be girls (Table II). Adults and children who were overweight or obese were less likely to have more than a high school education than normal-weight patients (Tables I and II). Inhaled corticosteroids were dispensed to 63%-70% of patients during the 2009 outcome year. Although the prevalence of inhaled corticosteroid dispensing was statistically different among the BMI categories in adults, the differences did not appear to be clinically significant (Table I).

Unadjusted relationships of BMI status to season of exacerbation

Exacerbations were more common in the fall and winter than in the spring and summer in all the patients (Tables III and IV). There was a significant linear increase with BMI category in the proportion of adult patients with any year 2009 exacerbations and exacerbations within each 2009 season, with the strongest relationship in the winter (Table III). There was a significant increase with higher BMI category in the proportion of children with any year 2009 exacerbations, and exacerbations within the fall and winter (Table IV).

Adjusted relationships of BMI status to season of exacerbation

Adults who were overweight or obese had a significantly increased risk of exacerbations in the fall and winter (but not in the spring and summer) after adjusting for age, sex, and education (Table V). Children who were overweight or obese also experienced a significantly increased risk of exacerbations in the fall and winter (but not in the spring and summer) after adjusting for sex and education (Table V).

TABLE IV. Relationship of BMI status in 2008 to exacerbations in 2009: children aged 5-17 y

BMI	% 2009 Exacerbations				
	Any	Fall	Winter	Spring	Summer
Normal (n = 5790)	15.5	6.0	5.2	4.4	3.4
Overweight (n = 1908)	18.7	8.2	6.2	4.5	4.0
Obese (n = 3002)	17.8	6.7	6.3	5.2	4.3
P value*	<.001	<.01	<.05	.26	.11

* χ^2 test.

In the GEE models, overweight or obese status was associated with increased exacerbations in both adults (odds ratio 1.28 [95% CI, 1.17-1.40]) and children (odds ratio 1.17 [95% CI, 1.07-1.29]) after controlling for season, age (in adults only), sex, and education (Table VI). Independent of BMI status, exacerbations were associated in both adults and children with spring, fall, and winter seasons, most prominently during fall and winter (Table VI). However, the interaction terms between BMI and season were not statistically significant in either adults ($P = .12$) or children ($P = .83$).

Because the fall and winter both appeared to confer increased risk, and because respiratory infections are frequent triggers of exacerbations in both seasons, the GEE models were repeated with season terms expressed as fall-winter versus spring-summer. In adults, there was a significant interaction between BMI status and season ($P = .03$) (Table VII). A higher BMI value increased the risk of exacerbations in the spring or summer, and normal-weight patients were more likely to experience exacerbations in the fall or winter. However, patients who were overweight or obese were particularly likely to experience exacerbations in the fall and winter (Table VII). By contrast, no significant interaction ($P = .97$) was demonstrated in children between BMI status and fall-winter versus spring-summer seasons in the prediction of exacerbations.

DISCUSSION

Prior studies demonstrated a relationship between increased BMI value and an increased risk of asthma exacerbations in both children and adults³⁻⁵ but have not addressed whether these relationships vary by season. The current study confirms an increased risk of asthma exacerbations in patients of all ages with higher BMI values and extends prior observations to show that this increased risk applies to exacerbations in all seasons in adults and to exacerbations in fall and winter in children (Tables III and IV). Moreover, the current study showed that, when the risks are adjusted for sex and education, the relationships to fall and winter exacerbations remain significant in adults and children (Table V). Finally, in adults only, and consistent with our *a priori* hypothesis, analysis of the data demonstrates a significant interaction between BMI status and season, such that adults who are overweight or obese and with asthma are particularly likely to experience exacerbations in the fall or winter (Table VII). These findings are consistent with the previously observed relationship between increased BMI value and viral-induced asthma exacerbations.⁵

The relationships between overweight and obese status and increased asthma morbidity is likely multifactorial in etiology.¹ The seasonal findings of the current study support a role for vitamin D insufficiency, which could be mediated by the

TABLE V. Adjusted relationships (OR [95% CI]) between season-specific exacerbations and BMI status (overweight or obese vs normal weight)*

	Spring	Summer	Fall	Winter
Adults	1.16 (0.99-1.37)	1.14 (0.96-1.35)	1.34 (1.16-1.55)†	1.41 (1.22-1.64)†
Children	1.08 (0.91-1.29)	1.22 (1.01-1.48)†	1.21 (1.05-1.40)†	

OR, Odds ratio.

*Log binomial model adjusted for sex, education, and age in adults.

†Significant ($P < .05$) results.

TABLE VI. Independent effects of BMI status (overweight or obese vs normal weight) and season on exacerbations*†

BMI status, relative risk (95% CI)	Season (compared with summer), relative risk (95% CI)		
	Spring	Fall	Winter
Adults	1.28 (1.17-1.40)	1.11 (1.02-1.21)	1.49 (1.38-1.61)
Children	1.17 (1.07-1.29)	1.22 (1.08-1.38)	1.74 (1.55-1.95)

*The GEE model also was adjusted for sex, education, and age (in adults); the results shown are for the models without the BMI by season interaction term.

†The P values for the interaction term were .12 for adults and .83 for children.

TABLE VII. Independent effects of BMI status (overweight or obese vs normal weight) and season (fall-winter vs spring-summer) on exacerbations in adults*

Season	BMI status	Relative Risk (95% CI)
Spring-summer	Normal weight	reference
Spring-summer	Overweight or obese	1.16 (1.03-1.31)
Fall-winter	Normal weight	1.19 (1.04-1.35)
Fall-winter	Overweight or obese	1.62 (1.44-1.82)

*GEE model also was adjusted for sex, education, and age; the results shown are for the models with the BMI by season interaction term; because the P value for the interaction term was .03, the results are presented separately for spring-summer and fall-winter seasons.

relationship of low vitamin D status to increased viral infections.⁷ The pathophysiology of this association may relate to the role of vitamin D in the activity of the innate immune system.^{17,18} In this regard, the significant interaction between BMI status and fall-winter season in adults but not children could be explained by better vitamin D status in children compared with adults, but we are not aware of relevant data to confirm this hypothesis in southern California patients with asthma.

Another potential mediator of the relationship between a higher BMI value and increased asthma morbidity is decreased corticosteroid responsiveness because several studies have associated obesity with decreased corticosteroid responsiveness.¹⁰⁻¹² One would not expect corticosteroid resistance to vary as much by season, so we believe that the results of the current study are less likely to be explained by this mechanism. However, the relationship of BMI category to exacerbations, independent of season, in the GEE models suggests a nonseasonal component to the BMI-related exacerbation risk, and reduced corticosteroid responsiveness may be related to this aspect of the risk. In addition, the 2 mechanisms are not mutually exclusive. The corticosteroid resistance may be “unmasked” by viral-induced increases in bronchial hyperreactivity. Alternatively, corticosteroid resistance may be important in patients who are obese and with exacerbations in the spring and summer, whereas low vitamin D status may be important in patients with exacerbations in the fall and winter. Finally, the 2 mechanisms may be

related because results of *in vitro* studies indicate that vitamin D supplementation can increase corticosteroid responsiveness.¹⁹⁻²¹ Other possible mechanisms for the relationship between obesity and increased asthma morbidity, such as obesity-associated inflammation or adiposity-related mechanical fat load,¹ would not be expected to vary by season. However, as with reduced corticosteroid responsiveness, these factors could enhance the asthmatic reaction to viral infections in patients who are obese.

The current study has 2 main clinical implications. First, it suggests that increased surveillance for asthma exacerbations is especially warranted during the fall and winter in patients who are overweight or obese. Second, it supports the hypothesis that vitamin D supplementation may reduce the risk of asthma exacerbations in patients who are overweight or obese, particularly those that occur during the fall and winter. This hypothesis needs to be tested in randomized controlled trials. Already 1 study of Japanese children²² demonstrated reduced asthma exacerbations with winter-time vitamin D supplementation, and another study, in Polish children,²³ has demonstrated a reduction in infection-induced asthma exacerbations with vitamin D supplementation. Comparable studies in adults are underway.

Strengths of the current study include the large sample size, longitudinal design, and stratification by age group. However, the study does have some potential limitations. First, serum 25-hydroxyvitamin D levels were not measured to directly confirm the hypothesis that vitamin D status may underlie at least some of the current observations. Second, the definition of persistent asthma was based on administrative data not on clinical criteria. However, we used standard HEDIS criteria¹⁵ for determining persistent asthma from administrative data, and we previously showed good concordance in our population between this HEDIS definition of persistent asthma and the diagnosis of persistent asthma derived from patient-completed questionnaires.²⁴ Third, the current study did not control for potential comorbidity confounders or effect modifiers of the relationship between increased BMI and asthma exacerbations, such as gastroesophageal reflux disease or diabetes. However, although these parameters can be associated with the exposure (higher BMI value), they would not be expected to be associated with the outcome of season-specific asthma exacerbations, which would be necessary for these characteristics to act as confounders in those analyses.

In summary, this study has shown a relationship between higher BMI value (both overweight and obesity) and an increased risk of asthma exacerbations, particularly those that occur in the fall and winter, in 28,000 adults and children with asthma. Indirect evidence from other studies supports low vitamin D status in patients with a higher BMI value as a mechanism for some of the season-specific observations, but confirmation by randomized controlled trials of vitamin D supplementation will be necessary to test this hypothesis and define its clinical importance.

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