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Depression Is More Common in Girls With Nonatopic Asthma

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Background: Asthma may increase the risk of comorbid depressive disorders in children. Children suffering from asthma or depression are more often overweight. We examined whether depression was more likely in children with atopic and nonatopic asthma, independent of abdominal adiposity.

Methods: A cross-sectional analysis was performed on data collected in the Study of Asthma, Genes, and Environment in Canada. Children aged 11 to 14 years were assessed by a pediatric allergist to confirm asthma, allergic rhinitis, and atopic dermatitis diagnosis. Atopic asthma was defined based on skin prick testing and allergic asthma based on the presence of allergic rhinitis or atopic dermatitis in addition to asthma. Depressive symptoms were assessed using the Children's Depression Inventory-Short Form. Data were analyzed using logistic regression modeling to determine likelihood of depression in children with asthma, stratified by gender and adjusting for ethnicity, waist circumference (WC), and atopy.

Results: Four hundred thirty-one children aged 11 to 14 years (136 with asthma and 295 without asthma) were studied. After adjusting for the covariates, girls who had nonatopic or nonallergic asthma were three times more likely to have comorbid depressive symptoms compared with healthy girls (OR, 2.84; 95% CI, 1.00-8.10; OR, 3.47; 95% CI, 1.30-9.25, respectively). For each 10-cm increase in WC of girls, our model showed a 39% to 56% increase in the chance of depression. In boys, neither asthma nor WC showed an association with depression.

Conclusions: We recommend all health practitioners who see girls with asthma or girls who are overweight watch for depressive symptoms and treat comorbid depression seriously.

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Abbreviations: CDI-S = Children's Depression Inventory-Short Form; SAGE = Study of Asthma, Genes, and Environment; WC = waist circumference

Asthma affects one in 10 North American teenage boys and girls and imposes a substantial cost to the health-care system.¹⁻³ It is often accompanied by mental health comorbidities, which further increase health-care costs.⁴ Comorbid depressive and anxiety disorders are twice as common in children and adolescents with asthma.⁵ Other conditions coexisting with asthma, such as allergic sensitization, atopic dermatitis, allergic rhinitis, and food hypersensitivity, have also been linked to depressive symptoms in children and adults.⁶⁻⁸ Since asthma comorbidity frequently leads to deterioration in asthma control and quality of life,^{9,10} recent asthma treatment guidelines recommend that all possible comorbid conditions should be diagnosed and managed.¹¹

Unfortunately, asthma comorbidities have generally been overlooked, underdiagnosed, and undertreated,

especially in children.^{10,12} The increasing prevalence of child and adolescent obesity,¹³ which is even more exaggerated in boys and girls with asthma,¹⁴ indicates that greater attention to asthma comorbidity in

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childhood is warranted. Although some studies have reported on comorbid anxiety and panic disorders in children with asthma,¹⁵ there is only scarce literature on the comorbidity of asthma with depression in children that accounts for variations in depression by overweight,¹⁶ gender, age, and ethnicity.^{12,17,18} No studies have described the extent of multiple comorbidities in North American children by asthma phenotype, yet nonatopic asthma is a common variant of asthma in adolescent girls.¹⁹ The objectives of this

study were to (1) determine whether children with atopic and nonatopic asthma are at increased risk for depression independent of their abdominal adiposity, and (2) report on the interrelationship between allergic symptoms, asthma, and depression status.

MATERIALS AND METHODS

This was a descriptive study of data collected in the Study of Asthma, Genes, and Environment (SAGE), a 1995 birth cohort study of 13,980 children in Manitoba, Canada. The SAGE study was approved by the University of Manitoba Human Research Ethics Board (H2002:078); its detailed methodology is described elsewhere.²⁰ From a mail-out survey of all households in the SAGE birth cohort, children with ($n = 246$) and without parent-reported asthma ($n = 477$, random selection of respondents in rural and urban areas) were recruited for the SAGE nested case-control study at age 7 to 10 years. This article reports on the cross-sectional data of 487 children seen again in 2007 to 2009 when they were 11 to 14 years old.

All children were examined by a pediatric allergist to confirm the diagnosis of asthma, which was based on the 2003 Canadian Pediatric Asthma Consensus Guidelines.²¹ As BMI is not always the best measure of overweight during childhood,²² waist circumference (WC) was selected as an indicator of abdominal adiposity. Waistline was defined as the midpoint of the distance between the lower costal margin and iliac crest. Six other covariates that might affect the asthma/depression association were included: age,¹⁷ ethnicity (First Nations, Métis, white, and other),¹⁸ atopy,⁶ atopic dermatitis, allergic rhinitis, and food allergy.^{7,8,23} Children with a positive skin prick test to at least one allergen (ie, tree pollen, weed pollen, ragweed, grass pollen, *Alternaria*, *Cladosporium*, *Penicillium*, house dust mites *Dermatophagoides pteronyssinus* and *Dermatophagoides farinae*, cockroach, cat, dog, feathers, and peanut) were labeled atopic. Asthma and atopy were combined into a four-category variable of atopic asthma, nonatopic asthma, atopy-no asthma, and no atopy or asthma. Atopic dermatitis and allergic rhinitis were diagnosed by the pediatric allergist based on history and physical examination. Food allergy was based on parental report. To test our secondary objective, we created a four-category allergic asthma variable, similar to the atopic asthma

measure. Children having asthma and a positive history of either atopic dermatitis or allergic rhinitis were labeled as allergic asthma.

Depressive symptoms were assessed using the Children's Depression Inventory-Short Form (CDI-S). The full Children's Depression Inventory is widely used to diagnose depression in children according to the *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition criteria.^{24,25} CDI-S²⁶ has a correlation of 0.89 with the full inventory, is a valid and reliable questionnaire for 7- to 17-year olds, and is used in research to identify children with depressive symptoms.²⁷⁻²⁹ This questionnaire is composed of 10 questions and required children to select one of three statements that most closely explained their feelings in the proceeding 2 weeks. Answers were scored on a three-point scale, where zero corresponded to no symptoms; the total score was calculated by adding the scores of all questions (range, 0-20). Depression was defined as CDI-S scores ≥ 2 (highest quartile of the population under study). All study children were from English-speaking families.

Data were analyzed using logistic regression in SPSS, version 18.0 software (SPSS Inc; Chicago, Illinois) to determine the likelihood of depression in children with asthma. Crude OR and OR adjusted for WC, sex, age, ethnicity, atopic status, and food allergy were determined. Asthma and atopy or allergy were tested as four-category variables and as two independent variables. Since prevalence of both asthma and depression vary by gender,^{17,30} models were run separately in boys and girls. We used purposeful stepwise selection to find the best model, retaining variables at the 95% level of confidence. The goodness of model fit was assessed using Hosmer and Lemeshow Test at $P > 0.05$.

RESULTS

A total of 487 children in the SAGE nested case-control study were seen at 11 to 14 years of age. Fifty-six children (11.4%) who did not complete the CDI-S questionnaire were excluded. The mean age of study children was 12.5 years; 56% were boys. Atopic asthma was found in 24% of boys and 21% of girls (Fig 1). Eleven percent of girls had nonatopic asthma, almost double that of boys, accounting for one-third of the asthma in girls at this age. One-third of children with asthma and almost one-half of the children with non-atopic asthma had depressive symptoms, a higher prevalence than children without asthma (Table 1).

Asthma was more prevalent in children who (1) were atopic, (2) had atopic dermatitis, allergic rhinitis, or food allergy, and (3) were white (Table 2). Depressive symptoms were more common among girls and in First Nations children. Mean WC was significantly higher among children with depressive symptoms. Age did not differ by asthma status or depressive symptoms (Table 2).

Depression and Atopic vs Nonatopic Asthma

In all children, the likelihood of having depressive symptoms was twice as high in those who had nonatopic asthma compared with those who did not have asthma or atopy (Table 3). This association remained significant after adjustment for the covariates of gender, ethnicity, and WC. Having atopic asthma or atopy

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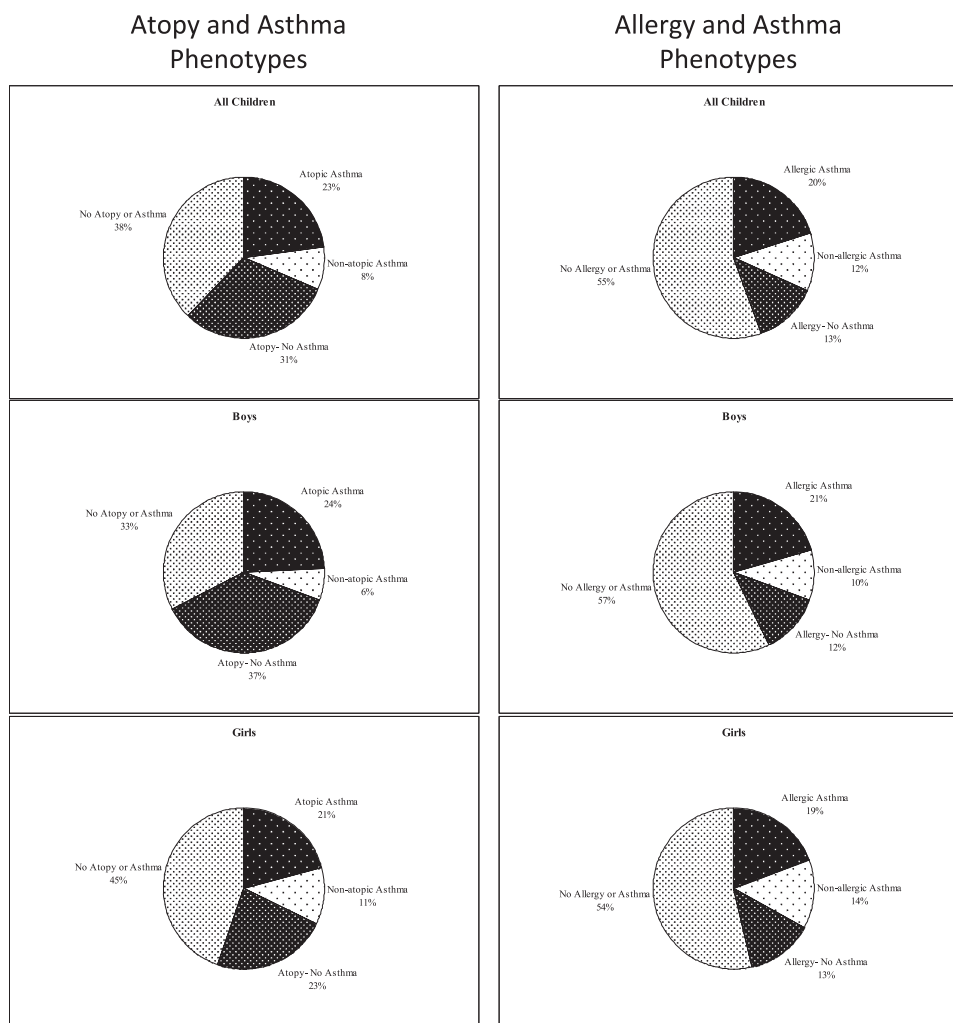


FIGURE 1. Distributions of asthma phenotypes within the study population.

without asthma did not increase the likelihood of depressive symptoms. In the same model, we observed a 22% increased risk of having depressive symptoms for each 10-cm increase in WC. In addition,

girls were 1.6 times more likely to be depressed compared with boys either before or after adjustment for asthma/atopy status, ethnicity, and WC. First Nations children were more than three times more likely to

Table 1—Distribution of Depressive Symptoms Among Children by Asthma Phenotypes

Asthma and Atopy Status	All Children		Depressive Symptoms		
	No.	%	No.	Prevalence, %	P Value
Asthma					.23
Yes	136	31.6	46	33.8	
No	295	68.4	83	28.1	
Atopy and asthma phenotypes					.15
Atopic asthma	97	22.8	29	29.9	
Nonatopic asthma	36	8.5	17	47.2	
Atopy-no asthma	131	30.8	37	28.2	
No atopy or asthma	161	37.9	46	28.6	
Allergy and asthma phenotypes					.13
Allergic asthma	86	20	24	27.9	
Nonallergic asthma	50	11.6	22	44.0	
Allergy-no asthma	55	12.8	17	30.9	
No allergy or asthma	240	55.7	66	27.5	

Table 2—Prevalence of Asthma and Depressive Symptoms Among Different Covariates

Covariates	All Children		Children With Asthma		<i>P</i> Value	Children With Depressive Symptoms		<i>P</i> Value
	No.	%	No.	Prevalence, %		No.	Prevalence, %	
Gender					.58			.02 ^a
Male	243	56.4	74	30.5		62	25.5	
Female	188	43.6	62	33.0		67	35.5	
Ethnicity					.002 ^b			.001 ^a
White	338	78.8	103	30.5		92	27.2	
First Nations	35	8.2	6	17.1		21	60.0	
Métis	32	7.5	12	37.5		8	25.0	
Other	24	5.6	15	62.5		8	33.3	
Atopy					<.001 ^b			.49
Yes	228	53.6	97	42.5		66	28.9	
No	197	46.4	36	18.3		63	32.0	
Atopic dermatitis					.02 ^b			.61
Yes	20	95.4	11	55.0		7	35.0	
No	411	4.6	125	30.4		122	29.7	
Allergic rhinitis					<.001 ^b			.78
Yes	131	69.6	83	63.4		38	29.1	
No	300	30.4	53	17.7		91	30.3	
Food allergy					<.001 ^b			.94
Yes	46	89.3	28	60.9		14	30.4	
No	385	10.7	108	28.1		115	29.9	
Age	12.5 ^d	11-14 ^e	12.5 ^d	...	.8	12.6 ^d	...	.34
WC (cm)	72.7 ^d	23-141 ^e	71.46 ^d	...	.5	75.99 ^d	...	.001 ^e

WC = waist circumference.

^aThe difference between the children with vs without depressive symptoms is statistically significant, using χ^2 test.

^bThe difference between the children with vs without asthma is statistically significant, using χ^2 test.

^cThe difference between the children with vs without depressive symptoms is statistically significant, using Student *t* test.

^dMean.

^eRange.

have depressive symptoms compared with white children (model 1).

Including asthma and atopy as two independent variables in model 2, we observed a slight increased

risk for depressive symptoms in the presence of asthma, but the OR was not statistically significant (model 2). Results for the other covariates remained similar to those in model 1. All models showed

Table 3—Association of Atopy and Asthma With Depression in All Children

Asthma Status and Covariates	Crude OR (95% CI)	Adjusted OR (95% CI) Model 1 ^a	Adjusted OR (95% CI) Model 2 ^b
Asthma	1.30 (0.84-2.02)	...	1.49 (0.92-2.40)
Atopy	0.87 (0.57-1.31)	...	0.95 (0.60-1.50)
Asthma/atopy			
No atopy or asthma	1.00	1.00	...
Atopy-no asthma	0.98 (0.59-1.64)	1.21 (0.70-2.08)	...
Nonatopic asthma	2.24 (1.07-4.68) ^c	2.47 (1.12-5.44) ^c	...
Atopic asthma	1.07 (0.61-1.85)	1.35 (0.75-2.43)	...
10-cm increase in WC	1.28 (1.10-1.49) ^c	1.22 (1.03-1.44) ^c	1.23 (1.05-1.45) ^c
Sex			
Male	1.00	1.00	1.00
Female	1.62 (1.07-2.45) ^c	1.64 (1.05-2.55) ^c	1.65 (1.06-2.56) ^c
Ethnicity			
White	1.00	1.00	1.00
First Nations	4.01 (1.96-8.22) ^c	3.42 (1.55-7.57) ^c	3.25 (1.48-7.14) ^c
Métis	0.89 (0.39-2.05)	0.80 (0.34-1.90)	0.80 (0.34-1.89)
Other	1.34 (0.55-3.23)	1.25 (0.50-3.13)	1.29 (0.52-3.23)

See Table 2 legend for expansion of abbreviation.

^aAdjusted for atopic/nonatopic asthma, WC, gender, and ethnicity.

^bAdjusted for asthma, atopy, WC, gender, and ethnicity.

^cThe association is statistically significant at *P* < .05.

goodness of fit at $P > .16$. Neither age nor food allergy showed a significant association with depressive symptoms or changed the association between this outcome and other variables. Thus, they were not retained in the final models for all children and in those stratified by gender.

Boys: The crude OR for depressive symptoms was 1.7 in boys with asthma and 1.8 in boys with nonatopic asthma compared with healthy boys, but was not statistically significant. WC was not associated with depression. First Nations boys had about a three times higher chance of experiencing depressive symptoms compared with their white peers (Table 4).

After adjusting for covariates in model 1, both atopic and nonatopic asthma increased the likelihood of depression, but neither reached statistical significance (model 1). The likelihood of depression rose to be twice as high in boys with asthma in model 2 and was almost statistically significant. The results for other covariates were equivalent in both models (Table 4). Goodness of fit was demonstrated in each model with $P > .89$.

Girls: Depressive symptoms were not more prevalent in girls who had asthma. Conversely, there was about 60% greater likelihood of depression for each 10-cm increase in WC of girls (Table 5). After adjusting for ethnicity and WC in model 1, we noted an increase in risk for depressive symptoms in girls with nonatopic asthma compared with healthy girls (model 1). The association between WC and depressive symptoms remained significant in this model. When including asthma and atopy as two separate variables in model 2, an association between asthma and depression was not apparent but remained for WC and depression (model 2). Similar to findings

in boys, First Nations ethnicity increased the risk for depression in girls in both models (Table 5). Goodness-of-fit P values for all models were $> .09$.

Depression and Allergic vs Nonallergic Asthma

As shown in Table 6, children who had nonallergic asthma were twice as likely to have comorbid depressive symptoms, independent of WC and ethnicity. In boys, nonallergic asthma did not show an association with depression before or after adjustments for covariates. These results were similar to what we observed in model 1. Finally, girls who had nonallergic asthma were 2.4 times more likely to have depressive symptoms. After adjusting for other covariates, this likelihood increased to 3.5 (model 3). Having allergic asthma did not increase the chance of comorbid depressive symptoms in boys or girls. The results for other covariates were similar to previous models reported in this study (data not shown).

DISCUSSION

In this community-based sample of > 400 Canadian children, those with nonatopic or nonallergic asthma were 2.5 times more likely to experience depressive symptoms compared with healthy children. This association was not found with atopic or allergic asthma. Depressive symptoms were 3.5-fold more likely in girls with nonallergic asthma. All associations were independent of WC, which itself increased depressive symptoms by a magnitude of 40% with each 10-cm increase in the WC of girls. In boys, on the other hand, neither asthma nor WC was correlated with depressive symptoms. A link between asthma and depression or overweight in childhood has previously been reported.^{5,14} Our findings on depression as

Table 4—Association of Atopy and Asthma With Depression in Boys

Asthma Status and Covariates	Crude OR (95% CI)	Adjusted OR (95% CI) Model 1 ^a	Adjusted OR (95% CI) Model 2 ^b
Asthma	1.65 (0.90-3.03)	...	1.92 (0.99-3.71)
Atopy	0.77 (0.43-1.39)	...	0.75 (0.39-1.44)
Asthma/atopy			
No atopy or asthma	1.00	1.00	...
Atopy-no asthma	0.65 (0.31-1.35)	0.76 (0.35-1.64)	...
Nonatopic asthma	1.81 (0.57-5.70)	1.95 (0.58-6.51)	...
Atopic asthma	1.22 (0.58-2.58)	1.45 (0.65-3.22)	...
10-cm increase in WC	1.18 (0.97-1.43)	1.10 (0.89-1.36)	1.10 (0.89-1.36)
Ethnicity			
White	1.00	1.00	1.00
First Nations	3.29 (1.17-9.26) ^d	3.35 (1.03-10.85) ^c	3.34 (1.03-10.81) ^c
Métis	0.94 (0.29-3.00)	0.87 (0.26-2.89)	0.87 (0.26-2.89)
Other	1.83 (0.58-5.73)	1.58 (0.48-5.15)	1.58 (0.48-5.12)

See Table 2 legend for expansion of abbreviation.

^aAdjusted for atopic/nonatopic asthma, WC, and ethnicity.

^bAdjusted for asthma, atopy, WC, and ethnicity.

^cThe association is statistically significant at $P < .05$.

Table 5—Association of Atopy and Asthma With Depression in Girls

Asthma Status and Covariates	Crude OR (95% CI)	Adjusted OR (95% CI) Model 1 ^a	Adjusted OR (95% CI) Model 2 ^b
Asthma	0.99 (0.52-1.87)	...	1.15 (0.56-2.34)
Atopy	1.15 (0.63-2.10)	...	1.20 (0.62-2.33)
Asthma/atopy			
No atopy or asthma	1.00	1.00	...
Atopy-no asthma	2.02 (0.94-4.32)	2.07 (0.92-4.64)	...
Nonatopic asthma	2.55 (0.96-6.77)	2.84 (1.00-8.10) ^c	...
Atopic asthma	0.91 (0.39-2.11)	1.10 (0.45-2.71)	...
10-cm increase in WC	1.56 (1.20-2.03) ^c	1.38 (1.05-1.83) ^c	1.46 (1.12-1.92) ^c
Ethnicity			
White	1.00	1.00	1.00
First Nations	4.52 (1.62-12.63) ^c	3.62 (1.19-11.05) ^c	3.17 (1.06-9.46) ^c
Métis	0.83 (0.25-2.80)	0.77 (0.21-2.83)	0.71 (0.20-2.53)
Other	0.89 (0.22-3.61)	1.14 (0.26-5.03)	1.13 (0.26-4.91)

See Table 2 legend for expansion of abbreviation.

^aAdjusted for atopic/nonatopic asthma, WC, and ethnicity.

^bAdjusted for asthma, atopy, WC, and ethnicity.

^cThe association is statistically significant at $P < .05$.

a common, independent comorbidity in a specific childhood asthma phenotype are new. We posit two hypotheses to explain these observations: the psychosocial thesis and the physiopathologic pathway.

Overweight in girls is becoming an important risk factor for depression.^{16,31} Mass media endorsements of skinny bodies for females and strong athletic bodies for males are known to affect youths' self-esteem and body image, especially in girls.^{32,33} Body dissatisfaction has been linked to negative mood in adolescent girls.³⁴ Personal image is also affected by having a condition like asthma and represents the basis for our psychosocial thesis. Children with asthma experience emotional burden or depression from the embarrassment of needing to curtail activities or use asthma medication in front of peers.³⁵ Embarrassment, sadness, loneliness, and "missing out on life" are commonly voiced by adolescents with asthma during focus group discussions.³⁶ In a qualitative study of children with asthma in the SAGE cohort, embarrassment in taking asthma medication and the need to limit activities was reported.³³ Limited participation in physical activities and even social activities may lower self-esteem in children with asthma.³⁷

When we implemented an asthma phenotype measure based on asthma and atopy status, only nonatopic asthma was associated with depressive symptoms in girls. Since both atopic and nonatopic asthma have a similar impact on quality of life,³⁸ psychosocial explanations for depression are unlikely to differ by asthma phenotype. An explanation specific to nonatopic asthma is required. Furthermore, since atopic dermatitis and allergic rhinitis are symptomatic conditions that affect quality of life,^{7,23} we anticipated a higher likelihood of depressive symptoms among children with asthma with these allergic conditions. In our study, a greater burden of allergic disease did not increase risk for depression. These unexpected results motivated us to search for an underlying physiopathologic pathway for nonatopic asthma in adolescence which, like in our study, is more dominant in girls.

Leptin may be the key hormone in the physiopathologic explanation. This adipocytokine is a bioactive protein mainly secreted from adipose tissue, although leptin receptors have been detected in lung tissue.³⁹ Leptin has been proposed to play a role in the pathogenesis of both overweight and asthma in adolescents.⁴⁰ Numerous studies have documented

Table 6—Association of Allergic Asthma With Depression

Asthma Status	Crude OR (95% CI)			Adjusted OR (95% CI) Model 3		
	All Children	Boys	Girls	All Children ^a	Boys ^b	Girls ^b
No allergy or asthma	1.00	1.00	1.00	1.00	1.00	1.00
Allergy-no asthma	1.18 (0.62-2.23)	0.64 (0.23-1.81)	1.90 (0.78-4.62)	1.41 (0.72-2.74)	0.78 (0.27-2.24)	2.18 (0.85-5.59)
Nonallergic asthma	2.07 (1.11-3.87) ^c	1.61 (0.63-4.09)	2.40 (1.001-5.77) ^c	2.34 (1.19-4.58) ^c	1.64 (0.61-4.37)	3.47 (1.30-9.25) ^c
Allergic asthma	1.02 (0.59-1.77)	1.51 (0.74-3.08)	0.59 (0.24-1.43)	1.19 (0.67-2.12)	1.73 (0.83-3.64)	0.67 (0.26-1.71)

See Table 2 legend for expansion of abbreviation.

^aAdjusted for allergic/nonallergic asthma, gender, ethnicity, and WC.

^bAdjusted for allergic/nonallergic asthma, ethnicity, and WC.

^cThe association is statistically significant at $P < .05$.

higher leptin levels in both children and adults with asthma,^{41,42} but few have tested associations by asthma phenotype. Nagel et al⁴³ found that elevated leptin levels in children were associated with a fivefold higher likelihood of nonatopic (but not atopic) asthma in children; similar to our results for depression in non-atopic asthma, this association was stronger in girls. Higher leptin levels have also been observed in individuals who present with depressive symptoms.⁴⁴ Considering the association between leptin levels and nonatopic but not atopic asthma in girls, and also with depressive symptoms, leptin secretion is a potential link between these two conditions in girls. Further studies are required to investigate this hypothesis.

Our study has a number of strengths. It was the first study to our knowledge to examine the association between asthma phenotype and depression in children while accounting for abdominal adiposity, gender, and ethnicity. The study population was large compared with previous studies.¹⁵ Asthma, atopic dermatitis, and allergic rhinitis were diagnosed by a physician, and atopy status was determined from skin prick testing. Depressive symptoms were based on the CDI-S, which has been validated against the full depression inventory.⁴⁵ Although the CDI-S is highly correlated with the full inventory, it has no fixed cutoff for depression. Thus, we were mindful of reporting our findings from the upper quartile cutoff as depressive symptoms and not depression. A major limitation of this study is the cross-sectional design, which does not allow us to examine the temporal relationship between asthma and depression. Future studies with longitudinal follow-up of children with and without asthma are needed. Worthy of study are proposed interrelationships between leptin levels, asthma, overweight, and depression.

Depression is an important comorbidity to diagnose and treat in children with asthma, because untreated depression results in decreased quality of life, impaired functional status, and poor asthma outcome.^{46,47} Comorbidity of asthma with depression leads to higher health-care use and costs beyond asthma itself, either for asthma or nonasthma symptoms.^{4,48} Although these extra costs can be reduced by early diagnosis and treatment of comorbid depression, depression is usually undiagnosed and untreated in children.¹⁰ Further, once depression has been diagnosed, <20% of asthmatic children receive adequate treatment with antidepressant medications.⁴⁹ Our study reports that girls with nonatopic asthma are about three times more likely to have depression independent of overweight status. Thus, we recommend all health practitioners who see girls with asthma watch for depressive symptoms and treat comorbid depression seriously.

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Author contributions: Dr Bahreinian had complete access to all study data and assumes responsibility for its integrity and accuracy.

Dr Bahreinian: contributed to conception, design, and acquisition of data; performed the main data analysis and interpretation; wrote and revised the submitted article; and provided final approval of the version to be published.

Dr Ball: contributed to conception and design, acquisition of data, and analysis and interpretation of data; revised the submitted article critically for important intellectual content; and provided final approval of the version to be published.

Dr Colman: contributed to the analysis and interpretation of data, revised the submitted article critically for important intellectual content, and provided final approval of the version to be published.

Dr Becker: contributed as principal investigator for the SAGE study on which the manuscript was based; made substantial contributions to conception and design, acquisition of data, and analysis and interpretation of data; revised the submitted article critically for important intellectual content; and provided final approval of the version to be published.

Dr Kozyski: contributed to conception and design, acquisition of data, and analysis and interpretation of data; revised the submitted article critically for important intellectual content; and provided final approval of the version to be published.

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