

**ASTHMA**

# Association between leptin and asthma in adults

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**Background:** Leptin, a pro-inflammatory cytokine produced by adipose tissue, has previously been shown to be associated with asthma in children. We hypothesised that high serum leptin concentrations would also be associated with asthma in adults.

**Methods:** The Third National Health and Nutrition Examination Survey is a cross sectional study that included fasting serum leptin concentrations and self-report of doctor diagnosed asthma. Data were analysed using multivariable logistic regression analysis.

**Results:** Of 5876 participants, those with current asthma had a higher mean unadjusted leptin concentration than those who had never had asthma (geometric mean (SE) 9.2 (0.6) µg/l v 7.6 (0.2) µg/l; p=0.02). After adjustment for triceps skinfold thickness and other covariates, the association between leptin and asthma appeared stronger in women than in men, and in premenopausal women than in postmenopausal women. Body mass index (BMI) was also associated with current asthma in women, but this association was not significantly affected by adjustment for leptin concentrations.

**Conclusions:** The results of this large population based study support the hypothesis that leptin is associated with asthma in women. In addition, while BMI also is related to asthma in women, this study does not support the suggestion that leptin contributes significantly to this association.

Several studies have shown an association between obesity and asthma,<sup>1-18</sup> and some have noted that this association may be stronger in women than in men.<sup>4 5 7 8 19-25</sup> Leptin, the protein product of the obesity (*ob*) gene, is synthesised and secreted by adipocytes.<sup>26</sup> Serum leptin levels are strongly correlated with measures of body fat including body mass index (BMI) and skinfold thickness, especially in women.<sup>26-29</sup> Although its physiological role is incompletely understood, leptin binds to receptors in the hypothalamus and influences the expression of several neuropeptides that regulate energy intake, energy expenditure, and neuroendocrine function. Leptin also regulates immune function and is believed to be pro-inflammatory.<sup>30 31</sup> Leptin concentrations are increased with oestrogen and progesterone treatment in women,<sup>32</sup> infectious and inflammatory states,<sup>30 33</sup> and during pregnancy.<sup>34</sup> Recent studies also suggest that serum leptin concentrations are a predictive factor for asthma in children, especially in boys, independent of BMI.<sup>35</sup>

Despite this evidence, little is known about the association between leptin concentrations and asthma in adults. We hypothesised that high serum leptin concentrations in adults would be associated with asthma and that this association would be stronger in women. We tested this hypothesis in a large, population based, cross sectional study.

## METHODS

### Cross sectional study

The Third National Health and Nutrition Examination Survey (NHANES III) which was carried out from 1988 to 1994 was designed to provide estimates of the health and nutritional status of the civilian non-institutionalised population of the United States.<sup>36</sup> Participants were selected using a stratified multistage sampling design and were initially interviewed at home; those who accepted an invitation to attend a mobile examination centre were asked to complete additional questionnaires, to undergo a variety of examinations, and to provide a blood specimen.

The study was performed at the Centers for Disease Control and Prevention, Atlanta, GA, USA. This was an anonymous

secondary data analysis and no subject identifiers were used. Permission was obtained from the Centers for Disease Control and Prevention, Atlanta, GA, USA and patient consent was obtained for participation and analysis in the original data set.

### Leptin concentrations

Early morning serum leptin concentrations (in µg/l) were obtained after an overnight fast of at least 8 hours. Data on the leptin concentrations of 6415 participants aged 20 years or older were available.<sup>37</sup>

The laboratory analysis for serum leptin was performed by Lingo Research Inc (St Louis, MO, USA) using a radioimmunoassay with a polyclonal antibody raised in rabbits against highly purified recombinant human leptin. The minimal detectable concentration of this assay was 0.5 µg/l and the limit of linearity was 100 µg/l. Intra- and inter-assay coefficients of variation were both less than 5%.<sup>37</sup>

### Assessment of asthma

Asthma was epidemiologically defined, based on two questions:<sup>36</sup> (1) "Has a doctor ever told you that you had asthma?" and (2) "Do you still have asthma?" Based on the answers to these questions, persons were divided into current asthma (defined as "yes" to both questions) and never asthma (defined as "no" to both questions).

### Covariates

The covariates included age, sex, race/ethnicity, educational status, self-reported smoking status, serum cotinine, BMI, triceps skinfold thickness, physical activity, and atopy status. Smoking status was assessed in two ways – self-report and a measured serum cotinine value. The triceps skinfold thickness was measured in duplicate at the midpoint of the right posterior upper arm using skinfold calipers (Holtain Ltd, Crymmych, UK). In previous studies triceps skinfold thick-

**Abbreviations:** BMI, body mass index; CDC, Centers for Disease Control and Prevention; MET, metabolic equivalent; NHANES III, Third National Health and Nutrition Examination Survey

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ness has been shown to be a useful field surrogate for measurement of body fat<sup>38, 39</sup> whereas BMI does not distinguish fat weight from non-fat weight.<sup>39</sup> A measure of physical activity was created by summing the products of the frequency of participation by the metabolic equivalent (MET) levels for each reported activity. Atopy was defined as an affirmative response to the question: "Has a doctor ever told you that you had hay fever?", a case definition from a previous NHANES analysis.<sup>40</sup>

### Menopausal status

Menopause was used as a surrogate marker for a women's reproductive hormonal status, with cycling of oestrogen and progesterone levels being present in actively menstruating women but not in postmenopausal women. Menopause was defined as an age of at least 60 years, or not having a menstrual cycle during the previous 12 months, or having a history of bilateral oophorectomy, or the absence of menses due to chemotherapy or radiation therapy based upon the NHANES III questionnaire.

### Statistical analysis

For statistical analysis, SAS Version 8.2 (Cary, NC, USA) and SUDAAN release 8.0 (Research Triangle Park, NC, USA) were used. SUDAAN was used to take into account the complex sampling design of the survey and provide appropriate standard errors. Sex specific quartiles of concentration of leptin were created. We carried out univariate analyses (to calculate frequency distributions), bivariate analyses (such as  $\chi^2$ ) and multivariable logistic regression analyses using asthma status (current *v* never) as the dependent variable. Consistent with our a priori hypothesis, we examined subgroups defined by sex, age and menopausal status, and performed formal tests for interaction. A two sided p value of <0.05 was considered statistically significant.

### RESULTS

A total of 5876 subjects participated in the study after exclusion of those who were either pregnant or had missing values for covariates. All were at least 20 years old, had attended the NHANES III morning mobile examination centre session, and had fasted for at least 8 hours before blood was drawn to measure their leptin concentrations. Of these participants, 290 (4.9%) currently had asthma and 5586 (95.1%) had never had asthma. The mean serum leptin concentration was 11.3  $\mu\text{g/l}$  (range 0.5–192.5, median 7.7). The Pearson correlation coefficient between the log trans-

formed concentration of leptin and triceps skinfold thickness (0.81) was higher than that for BMI (0.57).

Table 1 shows the characteristics of the study participants according to asthma status. Mean BMI and triceps skinfold thickness were higher in those who had current asthma than in those who had never had asthma. In order to understand these findings better the analyses were repeated stratified by sex.

In men the mean BMI in those who had current asthma (27.6  $\text{kg/m}^2$ ) was not significantly different from those who had never had asthma (26.6  $\text{kg/m}^2$ ,  $p = 0.23$ ). The mean triceps skinfold thickness in men with current asthma (13.3 mm) was also not significantly different from those who had never had asthma (13.3 mm,  $p = 0.95$ ).

On the other hand, in women the mean BMI in those who had current asthma (27.9  $\text{kg/m}^2$ ) was significantly higher than in those who had never had asthma (26.2  $\text{kg/m}^2$ ,  $p = 0.04$ ), but the mean triceps skinfold thickness in those who had current asthma (24.7 mm) was not significantly different from those who had never had asthma (23.9 mm,  $p = 0.46$ ). This unadjusted analysis shows that BMI, but not triceps skinfold thickness, was associated with current asthma in women. This association between BMI and current asthma in women persisted after adjustment in a multivariable logistic regression analysis for age, sex, race/ethnicity, educational status, smoking status, concentration of cotinine, physical activity, and atopy (table 2, model 1). Additional adjustment for serum leptin concentrations in this model did not significantly affect the association (table 2, model 2).

Table 1 also shows that mean unadjusted leptin concentrations were higher in participants who had current asthma than in those who had never had asthma. Similarly, the geometric mean (SE) concentrations of leptin were higher in participants who had current asthma (9.2 (0.6)  $\mu\text{g/l}$ ) than in those who had never had asthma (7.6 (0.2)  $\mu\text{g/l}$ ,  $p = 0.02$ ).

Adults with the highest quartile of leptin concentrations had an odds ratio (OR) of 1.56 (95% CI 0.96 to 2.53) for current asthma after adjustment in a multivariable logistic regression analysis for age, sex, race/ethnicity, educational status, smoking status, concentration of cotinine, physical activity, and atopy (table 3, model 1). This association was stronger in women (OR 1.85) than in men (OR 1.27). In women, adjustment for triceps skinfold thickness strengthened the association between serum leptin concentrations and asthma (table 3, model 2) while adjustment for BMI weakened this association (table 3, model 3).

**Table 1** Selected characteristics according to asthma status of 5876 study participants aged  $\geq 20$  years (NHANES III, 1988–1994)

Characteristic	Asthma status		p value
	Current (n = 290)	Never (n = 5586)	
	Mean or % (SE)	Mean or % (SE)	
Age (years)	43.6 (1.2)	44.4 (0.7)	0.61
Male (%)	39.9 (4.2)	48.5 (1.0)	0.07
White (%)	79.7 (3.5)	77.0 (1.6)	0.44
Education (years)	12.3 (0.2)	12.4 (0.1)	0.53
Current smoker (%)	34.1 (3.6)	27.2 (1.1)	0.09
Serum cotinine (ng/ml)	78.6 (10.3)	73.5 (2.8)	0.62
Body mass index ( $\text{kg/m}^2$ )	27.8 (0.6)	26.4 (0.2)	0.03
Triceps skinfold thickness (mm)	20.2 (0.7)	18.7 (0.2)	0.04
Physical activity (MET frequency)	110.0 (16.1)	112.2 (4.4)	0.89
History of diabetes (%)	5.7 (1.6)	3.7 (0.3)	0.23
Presence of domestic pets (%)	49.9 (3.8)	41.5 (1.3)	0.04
History of atopy (%)	40.0 (4.2)	9.9 (0.7)	<0.01
Leptin concentration ( $\mu\text{g/l}$ , unadjusted)	13.7 (0.9)	11.1 (0.3)	<0.01

MET, metabolic equivalent (a unit of expended energy).

**Table 2** Association between anthropometric measures of obesity and asthma in study participants aged  $\geq 20$  years stratified by sex (NHANES III, 1988–1994)\*

	Total			Men			Women		
	n	Regression coefficient (SE)	p value Wald $\chi^2$	n	Regression coefficient (SE)	p value Wald $\chi^2$	n	Regression coefficient (SE)	p value Wald $\chi^2$
Model 1 (not adjusted for concentration of leptin)									
Triceps skinfold thickness (mm)	5876	0.01 (0.01)	0.67	2753	0.01 (0.03)	0.90	3123	0.01 (0.01)	0.70
Body mass index (kg/m <sup>2</sup> )	5871	0.04 (0.02)	0.02	2753	0.03 (0.03)	0.36	3118	0.05 (0.02)	<0.01
Model 2 (adjusted for concentration of leptin)									
Triceps skinfold thickness (mm)	5876	-0.02 (0.01)	0.14	2753	-0.01 (0.03)	0.75	3123	-0.03 (0.02)	0.05
Body mass index (kg/m <sup>2</sup> )	5871	0.04 (0.02)	0.03	2753	0.04 (0.03)	0.28	3118	0.04 (0.02)	0.07

\*Models adjusted for age, sex (except sex-specific models), race/ethnicity, educational status, smoking status, cotinine concentration, physical activity, and atopy.

When stratified by age over or under 50 years, the association between concentrations of leptin and current asthma was stronger among women aged 20–49 years (table 4). Because these results suggested that the association might have differed by menopausal status, we also calculated odds ratios for premenopausal and postmenopausal women (table 5). The association between concentrations of leptin and current asthma was stronger in premenopausal women than in postmenopausal women.

Although statistical power was limited, formal tests of interaction were performed to evaluate if sex, age category, or menopausal status changed the association between concentrations of leptin and asthma. The interaction between sex and concentrations of leptin on asthma was not statistically significant whether concentrations of leptin were modelled as quartiles (p (Wald  $\chi^2$ ) = 0.48) or as a continuous variable (p (Wald  $\chi^2$ ) = 0.37). The interaction between age category and concentrations of leptin on asthma was also not statistically significant when women and men were analysed separately, whether concentrations of leptin were modelled as quartiles (p (Wald  $\chi^2$ ) = 0.74 for women and 0.12 for men) or as a continuous variable (p (Wald  $\chi^2$ ) = 0.36 for women and 0.86 for men). The interaction between menopausal status and concentrations of leptin on asthma was also not statistically significant whether concentrations of leptin were

modelled as quartiles (p (Wald  $\chi^2$ ) = 0.39) or as a continuous variable (p (Wald  $\chi^2$ ) = 0.46).

## DISCUSSION

This study suggests that higher serum leptin concentrations are associated with current asthma in adults and that the relationship may be stronger in women than in men. This study also demonstrates three interesting facets of this relationship. Firstly, the association between concentrations of leptin and current asthma appeared stronger in premenopausal than in postmenopausal women. Secondly, adjusting for the two commonly used anthropometric measures of obesity (BMI and triceps skinfold thickness) yielded different results. BMI may confound the association between leptin and asthma, making the association appear larger than may be actually true. On the other hand, adjusting for triceps skinfold thickness does not explain the association of leptin with asthma either, which persists and becomes greater after adjusting for skinfold thickness. The reason for this difference is unclear. Finally, while BMI itself was associated with current asthma in women, this association was not much affected by adjustment for serum leptin concentrations. This suggests that the effect of BMI on asthma is not mediated by the leptin pathway alone and probably involves other mechanistic pathways.

**Table 3** Association between serum leptin concentrations and asthma in study participants aged  $\geq 20$  years stratified by sex (NHANES III, 1988–1994)

Leptin quartiles*	Total (n = 5876)		Men (n = 2753)		Women (n = 3123)	
	OR (95% CI)	p value Wald $\chi^2$	OR (95% CI)	p value Wald $\chi^2$	OR (95% CI)	p value Wald $\chi^2$
Model 1†						
Quartile 1 (reference)	1.00	0.06	1.00	0.20	1.00	0.08
Quartile 2	1.13 (0.69 to 1.86)		1.13 (0.55 to 2.33)		1.11 (0.44 to 2.82)	
Quartile 3	0.77 (0.45 to 1.30)		0.57 (0.29 to 1.15)		1.00 (0.48 to 2.09)	
Quartile 4	1.56 (0.96 to 2.53)		1.27 (0.50 to 3.20)		1.85 (1.01 to 3.39)	
Model 2‡						
Quartile 1 (reference)	1.00	0.14	1.00	0.75	1.00	0.05
Quartile 2	1.21 (0.72 to 2.03)		1.17 (0.53 to 2.59)		1.29 (0.48 to 3.44)	
Quartile 3	0.89 (0.50 to 1.56)		0.61 (0.27 to 1.34)		1.42 (0.60 to 3.35)	
Quartile 4	1.99 (1.12 to 3.51)		1.43 (0.46 to 4.44)		3.19 (1.33 to 7.65)	
Model 3§						
Quartile 1 (reference)	1.00	0.22	1.00	0.16	1.00	0.80
Quartile 2	1.05 (0.63 to 1.73)		1.04 (0.48 to 2.25)		1.03 (0.39 to 2.69)	
Quartile 3	0.64 (0.40 to 1.01)		0.49 (0.24 to 1.00)		0.82 (0.40 to 1.67)	
Quartile 4	1.05 (0.59 to 1.87)		0.90 (0.33 to 2.44)		1.21 (0.52 to 2.82)	

OR, odds ratio; CI, confidence interval.

\*For men, quartile 1 is  $\leq 2.6$ , quartile 2 is  $>2.6$ – $\leq 4.4$ , quartile 3 is  $>4.4$ – $\leq 7.3$ , and quartile 4 is  $>7.3$   $\mu\text{g/L}$ . For women, quartile 1 is  $\leq 7.7$ , quartile 2 is  $>7.7$ – $\leq 13.2$ , quartile 3 is  $>13.2$ – $\leq 21.9$ , and quartile 4 is  $>21.9$   $\mu\text{g/L}$ .

†Model 1, adjusted for age, sex (except sex-specific models), race/ethnicity, educational status, smoking status, cotinine concentration, physical activity, and atopy.

‡Model 2, adjusted for variables in model 1 plus triceps skinfold thickness.

§Model 3, adjusted for variables in model 1 plus body mass index. Sample sizes for model 3 are 5871 for all participants, 2753 for men, and 3118 for women.

**Table 4** Association between serum leptin concentration and asthma in study participants stratified by age (NHANES III, 1988–1994)

Leptin quartiles*	Men		Women	
	OR (95% CI)	p value Wald $\chi^2$	OR (95% CI)	p value Wald $\chi^2$
Age 20–49 years				
N	1584	0.37	1871	0.01
Quartile 1 (reference)†	1.00		1.00	
Quartile 2	0.99 (0.35 to 2.76)		1.84 (0.55 to 6.17)	
Quartile 3	0.48 (0.14 to 1.60)		2.21 (0.71 to 6.88)	
Quartile 4	1.48 (0.36 to 6.01)		6.34 (2.01 to 19.92)	
Age $\geq$ 50 years				
N	1169	0.24	1252	0.47
Quartile 1 (reference)†	1.00		1.00	
Quartile 2	3.04 (0.97 to 9.55)		0.61 (0.20 to 1.91)	
Quartile 3	1.82 (0.45 to 7.37)		0.64 (0.20 to 1.97)	
Quartile 4	2.93 (0.60 to 14.31)		1.11 (0.34 to 3.59)	
p value Wald $\chi^2$ for sex-specific interaction between age and quartiles of leptin concentration on asthma status	0.12		0.74	

\*For men, quartile 1 is  $\leq$ 2.6, quartile 2 is  $>$ 2.6– $\leq$ 4.4, quartile 3 is  $>$ 4.4– $\leq$ 7.3, and quartile 4 is  $>$ 7.3  $\mu$ g/l serum leptin. For women, quartile 1 is  $\leq$ 7.7, quartile 2 is  $>$ 7.7– $\leq$ 13.2, quartile 3 is  $>$ 13.2– $\leq$ 21.9, and quartile 4 is  $>$ 21.9  $\mu$ g/l serum leptin.

†Adjusted for age, race/ethnicity, educational status, smoking status, cotinine concentration, triceps skinfold thickness, physical activity, and atopy.

The effect of leptin on lung development and physiology is poorly understood, even though leptin receptors are present in high concentrations in acini of fetal and adult animal lungs.<sup>41</sup> Leptin is believed to play a role in the intrauterine, neonatal, and postnatal development of murine lung.<sup>42</sup> In addition, some data suggest that leptin concentrations are increased acutely during inflammation<sup>30–33</sup> and, in turn, promote inflammation.<sup>43–45</sup> Support for this comes from experiments showing a prompt dose dependent increase in serum leptin levels and leptin mRNA expression in the adipose tissue of mice following the administration of pro-inflammatory cytokines such as tumour necrosis factor  $\alpha$  (TNF- $\alpha$ ) and interleukin (IL)-1,<sup>30</sup> as well as demonstration of increased serum TNF- $\alpha$ , IL-6 and IL-12 levels and increased phagocytosis by macrophages on exogenous administration of leptin.<sup>45</sup> In wild type mice, administration of exogenous leptin augments ozone induced airway inflammation.<sup>43</sup> In humans, enhanced concentrations of leptin are related to soluble TNF receptor (sTNF-R) 55, a marker of pro-inflammatory status in patients with chronic obstructive pulmonary disease.<sup>31</sup> Guler *et al*<sup>35</sup> found that the median serum leptin concentrations of children (especially boys) were significantly higher in those with asthma than in healthy controls (3.53 *v* 2.26 ng/ml,  $p = 0.01$ ) even though there was no difference in BMI levels. In a study involving

children born with very low birth weight who subsequently became overweight, Mai *et al*<sup>46</sup> showed that current asthmatics had median leptin concentrations twice as high as children without current asthma (30.8 *v* 14.3 ng/ml,  $p = 0.14$ ), but this was not the case in non-overweight children. Taken together, prior studies suggest that leptin may potentially play an important role in the pathophysiology of asthma.

Serum leptin concentrations are also related to obesity.<sup>26–29–47</sup> For equivalent BMI, leptin concentrations are higher in women than in men.<sup>28–29</sup> In addition, obesity is associated with increased concentrations of acute phase proteins, suggesting a pro-inflammatory state.<sup>48–50</sup> In recent years obesity has been identified as a risk factor for asthma.<sup>1–18</sup> A prospective study suggested that an increase in weight leads to incident cases of asthma, independent of physical activity.<sup>5</sup> It is believed by some that a decrease in physical activity, particularly among the obese, may also play a role in the increased prevalence and severity of asthma.<sup>51–52</sup> While the causal pathway remains unknown, the explanations advanced for the association between obesity and asthma include mechanical effects such as lack of tidal stretch leading to latching of airway smooth muscle, immunological effects of pro-inflammatory cytokines, genetic, hormonal and

**Table 5** Association between serum leptin concentration and asthma in women aged  $\geq$ 20 years according to menopausal status (NHANES III, 1988–1994)

Leptin quartiles*	Premenopausal (n = 1701)		Postmenopausal (n = 1385)	
	OR (95% CI)	p value Wald $\chi^2$	OR (95% CI)	p value Wald $\chi^2$
Quartile 1 (reference)†	1.00	0.048	1.00	0.114
Quartile 2	1.80 (0.51 to 6.35)		0.60 (0.19 to 1.90)	
Quartile 3	1.69 (0.50 to 5.63)		1.06 (0.40 to 2.76)	
Quartile 4	3.56 (1.11 to 11.36)		2.16 (0.60 to 7.76)	

\*For women, quartile 1 is  $\leq$ 7.7, quartile 2 is  $>$ 7.7– $\leq$ 13.2, quartile 3 is  $>$ 13.2– $\leq$ 21.9, and quartile 4 is  $>$ 21.9  $\mu$ g/l serum leptin.

†Adjusted for age, race/ethnicity, educational status, smoking status, cotinine concentration, triceps skinfold thickness, physical activity, and atopy.

The interaction between menopausal status and concentrations of serum leptin modelled in quartiles on asthma status was not significant ( $p$  (Wald  $\chi^2$ ) = 0.39).

environmental effects such as change in dietary factors and increased exposure to indoor allergens.<sup>53 54</sup>

Some investigators have noted that the association between obesity and asthma may be stronger in women than in men, suggesting that reproductive hormones might be involved in the causal pathway.<sup>4 5 7 8 19–25</sup> In addition, Castro-Rodriguez *et al*<sup>7</sup> found this association to be stronger in girls whose puberty started before the age of 11 years than in girls whose puberty started later. Barr *et al*<sup>55</sup> showed that exogenous hormone replacement therapy in adult postmenopausal women was associated with an increased relative risk for asthma, with a positive dose-response between the daily dose of conjugated oestrogens and the risk of asthma. Similarly, administration of exogenous reproductive hormones to women has also been noted to increase serum leptin concentrations further.<sup>32</sup> These observations have led some to conclude that leptin may be important in explaining the link between obesity and asthma, particularly in women.

Our study does not support the assertion that leptin plays a dominant role in the association between obesity and asthma in women, but it does support the conclusion that leptin itself may play a part in asthma in women. This would be consistent with data obtained from previous animal and human studies.<sup>31 35 43 46</sup> Further relationships between asthma, leptin, and female reproductive hormones cannot be adequately addressed in this study because of the cross sectional design and inadequate sample size.

The study has some additional limitations. The definition of asthma was a self-reported doctor diagnosis of asthma, and this may result in some misclassification bias. Serum reproductive hormone concentrations were not measured nor were the leptin concentrations measured in relation to the day of the menstrual cycle in premenopausal women. Finally, in order to confirm definitively that leptin has a different effect on asthma status in various groups, a statistically significant interaction is required. It is not sufficient to observe a statistically significant relationship in one group and not in the other.<sup>56</sup> This exploratory analysis lacks the power to detect a statistically significant interaction and further work in larger cohorts is warranted.

In summary, using nationally representative data, this study has shown that higher serum leptin concentrations are associated with current asthma in women and that this association may be stronger in premenopausal women. In addition, while BMI is also associated with current asthma in women, this study does not confirm that leptin contributes significantly to this association. Future studies will need to confirm and expand on these observations to improve our understanding of the pathogenesis of asthma.

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